Chronic Urticaria: Diagnosis and Management

Flavia Hoyte, MD
Assistant Professor of Medicine
Division of Allergy and Immunology
National Jewish Health and University of Colorado
Disclosures

None
Outline

• Definitions
• Epidemiology & Natural History
• Diagnosis
• Therapy
• References
• Questions?
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 3\textsuperscript{rd}-5\textsuperscript{th} decades
- Spontaneous remission by 1 year = 30-50%
- Average duration of disease: 2-5 yrs
- Approx 20% 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)
  – Thyroid disease: 17
  – SLE: 7
  – CTD: 16
  – Cutaneous vasculitis: 60
  – Paraproteinemia: 3
• Similar to single site study from 2011

“Autoimmune” testing for CIU

- Autologous serum skin test
- Basophil CD203c expression – marker of activation
- CU index, or histamine release assay
- Identification of IgG against IgE or the IgE receptor (FcεR1α)
Autologous Serum Skin Test (ASST)

- Patient’s serum injected intradermally into patient; assess for wheal and flare
- Up to 50% of CU pts have + ASST at 30 minutes
- Not routinely used in practice because it:
  - Yields variable results even when clinical presentation is similar
  - Can be positive even without CU (in AR and even in normal controls, up to 37% of non-CIU pts)
  - Does not necessarily correlate with disease remission, especially with concomitant thyroiditis
  - Does not predict response to therapy or help guide therapeutic decisions

Basophil CD203c Assay

• CD203c is a basophil-specific marker of activation
• CD203c expression is thought to be IgG-mediated (25% reduced expression when IgG is depleted)
CU Index (histamine release assay)

- Patient serum incubated with donor basophils
- Value > 10 indicates significant histamine release
- Potential correlation between higher levels of CU index and antihistamine refractory disease (mean CU index of 10.6 vs 5.1) – controversial\(^1\)
- Limitations include: variability of results depending on unique characteristics of the donor basophils and lack of standardized reagents yielding low reproducibility
- No diff in skin bx of pts with high or low CU index \(^2,3\)
- No correlation btwn HRA positivity & clinical response to immunomodulatory medications \(^4\)

1. Lapolla et al 2012
2. Sabroe et al 1999
3. Ying et al 2002
CU index is often positive in non-CU pts

CU index is often positive in non-CU pts

Direct identification of antibodies

- Anti-IgE (10%) or Anti-FCER1α (30%) antibodies
- Can be detected by immunoenzymometric assay (IEMA)
- Positive antibodies do not correlate with commercially available CU index
- Autoantibodies can be found in normal controls and in pts with other autoimmune dz (SLE, dermatomyositis, pemphigoid, and pemphigus vulgaris)

No difference in antibody levels for CIU & non-CIU

Figure 1. Autoantibody levels in CIU and non-CIU subjects. (a) IgG anti-FcεRIα levels in CIU subjects and non-CIU subjects. (b) IgG anti-IgE levels in CIU and non-CIU subjects. CIU subjects are categorized based on basophil phenotype.

CU and autoimmunity

- The following autoimmune conditions have been found to be more prevalent in pts with CU:
  - Celiac disease
  - Thyroid disorders
  - Sjogren syndrome
  - SLE
  - RA
  - Type I DM
- ANA more prevalent in CU population
- Autoimmune disorder more likely to be diagnosed in the decade after the onset of CU, rather than before
Thyroid antibodies are more common in CU pts

- Thyroid antibodies include thyroid peroxidase and antimicrosomal antibodies
- Prevalence in CU patients = 12-30%
- Prevalence in general population = 5-10%
- Most pts with thyroid antibodies have nl fxn
- These antibodies may merely indicate a higher tendency to form autoantibodies
- One study suggests that CU pts with thyroid autoantibodies showed poor response to standard therapies and to have more persistent disease
Thyroid disorders are more common in CU pts

- 12700 CU pts compared with 10700 controls over 10 years
  - 10% CU vs 0.6% control have hypothyroidism
  - 2.6% CU vs 0.09% control have hyperthyroidism

- Timing of thyroid diagnosis
  - 20% before CU
  - 3-4% within first 6 months of CU dx
  - 80% within 10 years of CU dx

Treatment of CU pts who have thyroid antibodies

- If hypothyroid or hyperthyroid with thyroid antibodies, treat the underlying disease
- If euthyroid: controversial
  - Case studies show benefit\(^1\)
  - Small randomized trial showed no effect at 12 weeks\(^2\)

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
Therapy

• Education
• EAACI/GA(2)LEN/EDG/WAO Urticaria Guidelines
  – start with antihistamines
• Immunomodulators
• Omalizumab
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??
EAACI/GA(2)LEN/EDF/WAO Urticaria Guidelines

- Non-sedating H1 antihistamine (nsAH)*

- Increase dose of antihistamine (up to four-fold) **

- Add H2 antagonist, leukotriene antagonist OR change nsAH OR add sedating AH (sAH), Doxepin OR ketotifen ** (not available in US)

- Add immune suppressive agent (cyclosporine A **, mycofenolate mofetil, sulfasalazine, methotrexate dapsone hydroxychloroquine) or omalizumab

Systemic steroids as short burst for flares or as low dose chronic therapy if resistant to all of the above

Adapted from Zuberbier et al. Allergy 2014. 69(7): e1-e29.
Immunomodulators

- cyclosporine A
- mycofenolate mofetil
- sulfasalazine
- dapsone
- hydroxychloroquine
- prednisone
Treatment options based on skin biopsy

• Neutrophil predominant
  – Dapsone
  – Colchicine

• Lymphocyte-eosinophil
  – Sulfasalazine

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:**
  - 1990s: case reports
  - 2000: RCT placebo controlled (N=30) – 65% response at 4 weeks, with 26% remaining sx free at 20 weeks off CSA
  - 2006: RDBRPC of 16 wks vs 8 wks (N=99) – 63% response at 8 wks, no difference at 16 wks
  - 2010: dosing study of 120 pts – 62% response to CsA
- **Side effects** relatively common: GI sx, headache, parasthesias (>10%), infections, ??malignancy
- **Monitor:** BP and renal function regularly

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

• Antiinflammatory 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
• Lab monitoring: CBC, liver function testing & U/A monthly for first 3 months, then prn
• Recent 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

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

- Well-tolerated, widely available, inexpensive
- Sulfone antimicrobial; Has effects on PMN fxn and activation, hence its use in neutrophil predominant CU
- SE: peripheral neuropathy, methemoglobinemia, agranulocytosis, & allergic rxns like DRESS
- Lab monitoring: R/o G6PD deficiency before starting therapy; monitor Hb and LFTs
- One small randomized control study
  - 22 pts, crossover design: dapsone x 6 wks, placebo x 6 wks
  - Improved itch, visual analog scale score, urticaria score in dapsone group only
  - 3 had complete resolution of hives & itch; 31% had over 50% of hives resolve; 41% had over 50% resolution of itch

Hydroxychloroquine (HCQ)

- Safe, inexpensive, well-tolerated
- Monitoring: CBC, LFTs, eye exam, muscle strength
- 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

Omalizumab in CU

- Two doses approved by FDA: 150mg and 300mg every 4 weeks
- Dosing does NOT depend on IgE level
- No lab monitoring needed; generally well-tolerated (anaphylaxis 0.2%, local rxns 40%)
- Optimal dosing interval may range between 2 and 8 weeks between doses
- Optimal duration of therapy unknown
- No long-term disease modifying effects have been shown
- Resistance does not generally develop
Omalizumab mechanism of action

Omalizumab reduction of FcERI expression: basophils before mast cells

Beck et al. JACI 2004; 114: 527-530
Evidence for omalizumab in CU

• Case reports and case series

• Placebo-controlled trials:
  – 49 subjects with IgE autoantibody against thyroid peroxidase and persistent CU\(^1\)
  – Asteria II trial – 323 subject with CU resistant to H1 antihistamines\(^2\)
  – 335 subjects with CU resistant to H1 AH plus H2 AH/Anti-LT\(^3\)

Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria (Asteria II trial)

466 Patients were screened

146 (31%) Were excluded
18 (12%) Had contraindications to diphenhydramine
21 (14%) Had evidence of current drug or alcohol abuse
9 (6%) Missed diary entries in 7 days before randomization
48 (33%) Had other unspecified reasons
59 (34%) Had other reasons
3 (1%) Were rescreened

323 Underwent randomization

79 Were assigned to receive placebo
5 (6%) Withdrew from study
1 (1%) Had adverse event
3 (4%) Was lost to follow-up
3 (4%) Withdrawn or were withdrawn by guardian
74 (94%) Completed study

82 Were assigned to receive omalizumab, 75 mg
7 (9%) Withdrew from study
1 (1%) Was lost to follow-up
1 (1%) Was withdrawn by physician
4 (5%) Withdrawn or were withdrawn by guardian
1 (1%) Had disease progression
75 (91%) Completed study

83 Were assigned to receive omalizumab, 150 mg
9 (11%) Withdrew from study
1 (1%) Had adverse event
2 (2%) Were lost to follow-up
3 (4%) Withdrew or were withdrawn by guardian
3 (4%) Had disease progression
74 (89%) Completed study

79 Were assigned to receive omalizumab, 300 mg
1 Was not treated

12 (15%) Withdrew from study
1 (1%) Had adverse event
2 (3%) Were lost to follow-up
3 (4%) Withdrew or were withdrawn by guardian
6 (8%) Had disease progression
67 (85%) Completed study
Study Design – Asteria II

- Screening Period: 2 Weeks
- Treatment Period: 12 Weeks
- Follow-Up Period: 16 Weeks

- Treatment administered every 4 weeks for total of 3 doses: placebo or omalizumab (75, 150, or 300 mg)

- Week 12: primary endpoint assessment

- Patients on stable dose of H1 antihistamine throughout treatment period and were permitted rescue DPH 25 mg up to 3/day

N= 323

### Table 2. Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N=79)</th>
<th>Omalizumab</th>
<th>Omalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 mg (N=82)</td>
<td>150 mg (N=82)</td>
<td>300 mg (N=79)</td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itch-severity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to wk 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-5.1±6.6</td>
<td>-5.9±6.5</td>
<td>-8.1±6.4</td>
</tr>
<tr>
<td>Median (range)</td>
<td>-4.0 (-20.5 to 6.0)</td>
<td>-6.5 (-21.0 to 10.0)</td>
<td>-8.5 (-21.0 to 5.1)</td>
</tr>
<tr>
<td>Least-squares mean difference for treatment vs. placebo (95% CI)†</td>
<td>NA</td>
<td>-0.7 (-2.5 to 1.2)</td>
<td>-3.0 (-4.9 to -1.2) ‡</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
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<tr>
<td>Weekly no. of hives</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to week 12</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-5.2±6.0</td>
<td>-7.2±7.0</td>
<td>-9.8±7.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>-2.4 (-19.5 to 3.5)</td>
<td>-6.5 (-21.0 to 8.5)</td>
<td>-10.0 (-21.0 to 3.0)</td>
</tr>
<tr>
<td>Least-squares mean difference for treatment vs. placebo (95% CI)¶</td>
<td>NA</td>
<td>-2.0 (-4.1 to -0.1)</td>
<td>-4.5 (-6.7 to -2.4) §</td>
</tr>
<tr>
<td>Patients with UAS7 ≥6 at wk 12 — no. (%)</td>
<td>15 (19)</td>
<td>22 (27)</td>
<td>35 (43) ‡</td>
</tr>
<tr>
<td>Overall score on Dermatology Life Quality Index∥</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-6.1±7.5</td>
<td>-7.5±7.2</td>
<td>-8.3±6.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>-5.0 (-25.0 to 13.0)</td>
<td>-7.0 (-26.0 to 11.0)</td>
<td>-8.0 (-27.0 to 6.0)</td>
</tr>
<tr>
<td>Least-squares mean difference for treatment vs. placebo (95% CI)**</td>
<td>NA</td>
<td>-1.7 (-3.8 to 0.5)</td>
<td>-2.5 (-4.6 to -0.4) ††</td>
</tr>
<tr>
<td>Angioedema-free days from wk 4 through wk 12 — %‡‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>89.2±19.0</td>
<td>93.5±14.9</td>
<td>91.6±17.4</td>
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<tr>
<td>Median (range)</td>
<td>100.0 (15.4 to 100.0)</td>
<td>100.0 (30.4 to 100)</td>
<td>100.0 (14.3 to 100.0)</td>
</tr>
</tbody>
</table>
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.
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

References


References


References

CYCLOSPORINE:

MYCOPHENOLATE MOFETIL:
SULFASALAZINE:

HYDROXYCHLOROQUINE:

DAPSONE:
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