Refractory Chronic Urticaria: When Omalizumab Fails

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Disclosures

- Research Grants
  - NIH
- Honoraria
  - UpToDate, Genentech
- Consulting
  - Aimimmune (DSMB)
- Organizations:
  - Joint Task Force on Practice Parameters
  - AAAAI BOD

All medications other than antihistamines and omalizumab are considered "off-label" for treatment of chronic urticaria.

Objectives

- Gain an understanding of stepwise approach for urticaria and differences in guidelines
- Be able to discuss updates on omalizumab in urticaria and angioedema
- Gain an understanding of the use and risks of anti-inflammatory, immunosuppressant and other alternative therapies in refractory urticaria/angioedema.
70 yo with CIU

- 70 yo M with 20 yrs of episodic hives and 18 months of daily urticaria and frequent angioedema. No obvious triggers and prior lab work up negative.
- Currently on fexofenadine 180 bid and hydroxyzine 25 at bedtime without side effects or benefit
- On exam has scattered blanchable urticaria

Practice parameter

The diagnosis and management of acute and chronic urticaria: 2014 update

Chief Editors: Jonathan A. Bernstein, MD, David M. Long, MD, and David A. Khan, MD
Workgroup Co-Chairs: Timothy Craig, DO, David Dreyfus, MD, Paul Hebert, MD, Javed Sheth, MD, David Wilensky, MD, and Bruce Zwiren, MD

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Management of Refractory Chronic Urticaria

Step 6. IVX chlorpheniramine, 1 ml

Step 5. Consider immunomodulation: biological (e.g., abatacept in HLA-DR nonampullar Urticaria)

Step 4. Severe management (psychogenic, exogenous, endogenous). The addition of CBT.

Step 3. New treatments: oral or topical ocular depot corticosteroids, omalizumab, intramuscular heparin, or antihistamines.

Step 2. Prescribe (oral or topical) H1 receptor agonists (e.g., montelukast, leupobin). Identify and dechallenge the foods and medications that may be involved.

Step 1. New generation H1 antihistamines. The specificity of H1 receptor agonists.

Updosing Antihistamines When Standard Doses Fail

- 38% response rate to standard antihistamine dose
- 60% response rate to updosing of antihistamine; however, lots of heterogeneity and most studies of low quality
SUMMARY STATEMENT 78: Higher doses of second-generation antihistamines may provide more efficacy but data are limited and conflicting for certain agents. (B)
Predicting Response to Antihistamines Based on Histamine Wheal Suppression

150 CIU patients treated in blinded fashion with 5 different antihistamines or placebo

Large suppression of histamine wheal suggests good response to antihistamines

Step 3

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


Hydroxyzine and Doxepin

- Not therapeutically equivalent
- Which agent to choose?
  - Usually based on which one they haven't tried
  - Doxepin associated with weight gain and likely more sedating
- Dosing preferences
  - Usually 10-25 mg qhs as a single dose
  - Increase dose by 10-25 mg weekly as tolerated
  - Target of 50-150 mg qhs

Other Potential Problems with 1st Gen Antihistamines

Cumulative Use of Strong Anticholinergics and Incident Dementia
A Prospective Cohort Study

- 10-yr prospective study of Group Health data on 3434 subjects > 65 years
- Highest quartile of use had increased risk of dementia 1.54 (95%CI, 1.21-1.96)
- Based on data this would equate to > 3 years of treatment with:
  - Hydroxyzine 75 mg/d
  - Doxepin 10 mg/d
- Association, not causality

70 yo with CIU Epilogue

- Increased cetirizine to 20 bid and gradual escalation of hydroxyzine to 100 mg at bedtime with reduction from daily moderate-severe hives to < 1/week “nuisance hives” and no sedation
- Reduced meds to cetirizine 10 bid and hydroxyzine 75 at bedtime and stable
- In process of tapering further to maintain control

Take Home: Don’t forget/fear aggressive antihistamines

31 yo with CIU Refractory to AH and Omalizumab

- 31 yo woman with chronic urticaria for 1 year
- Prior laboratory work-up including autoantibodies negative, skin biopsy consistent with urticaria
- Failed:
  - cetirizine 40 mg/d
  - + desloratadine 5 mg bid
  - + ranitidine 300 mg/d
  - + montelukast
  - +hydroxyzine 150 mg/d

31 yo with CIU Refractory to AH and Omalizumab

- Treated with omalizumab 300 mg every 4 weeks for 6 months with no improvement
- Requires prednisone 20 mg/d to maintain low level of hive activity
  - Has gained 30 lbs due to prednisone
  - Frustrated and tearful during exam
  - Blanchable typical urticarial lesions
Approach to Refractory Urticaria

- Is it really urticaria/AE?
  - Have you seen the lesions?
  - Skin biopsy may be helpful (not always)
- What kind of work up is recommended?
- Is it really antihistamine resistant?
  - Aggressive dosing of 2nd and 1st generation antihistamines tried and failed?
- Has omalizumab failed?
  - How much?
  - How long?
  - How often?

Diagnostic Evaluation in Urticaria

How Many and What Tests Are Required?
SUMMARY STATEMENT 28: After a thorough history and physical examination, no diagnostic testing may be appropriate for patients with CU; however, limited routine lab testing may be performed to exclude underlying causes. Targeted lab testing based on clinical suspicion is appropriate. Extensive routine testing for exogenous and rare causes of CU, or immediate hypersensitivity skin testing for inhalants or foods, is not warranted.

Routine Labs

Summary Statement 28 (cont’d): Routine laboratory testing in patients with CU, whose history and physical examination lack atypical features, rarely yields clinically significant findings. [C]
Task Force Labs in CU Consensus

Laboratory Evaluation

- Routine evaluation. Testing should be selective. There is an honest difference of opinion concerning the appropriate tests that should routinely be performed for patients with CU in the absence of clinicologic considerations raised by a detailed history and careful physical exam.
- A majority of members of the Practice Parameters Task Force expressed a consensus for the following routine tests in managing a patient with CU without atypical features:
  - Complete blood count with differential
  - Erythrocyte sedimentation rate and/or C-reactive protein
  - Liver enzymes
  - Thyroid stimulating hormone

The utility of performing the above tests routinely for CU patients has not been established.

Additional Labs in CU

- Additional evaluation may be warranted based upon patient circumstances, and may include but not be limited to the diagnostic tests listed below. A thorough history and meticulous physical exam is essential for determining whether these additional tests are appropriate:
- Skin biopsy
- Physical challenge tests
- Complement system e.g. C3, C4, and CH50
- Stool analysis for ova and parasites
- Urinalysis
- Hepatitis B and C serologies
- Chest radiograph and/or other imaging studies
- Antinuclear antibody (ANA)
- Rheumatoid factor, anti-chitinase protein
- Cryoglobulin levels
- Serum and/or skin testing for immediate hypersensitivity
- Thyroid autoantibodies
- Serum protein electrophoresis
- More detailed laboratory testing and/or skin biopsy merits consideration if urticaria is not responding to therapy as anticipated.
- Additional laboratory testing may be required prior to initiation of certain medications, e.g. glucose-6-phosphate dehydrogenase (G6PD)

The EAACI/GA/LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria.

The 2017 Revision and Update

We recommend limited investigations. Basic tests include differential blood count and CRP and/or ESR.

(conensus-based)

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<table>
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<td></td>
<td>&gt; 90% consensus</td>
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In CU, we recommend performing further diagnostic studies based on the patient history and examination, especially in patients with long-standing and/or uncontrolled disease.

Allergy 2018 (in press)
Omalizumab in Chronic Urticaria

Efficacy/Dosing
Duration
Predicting Response
Physical Urticaria
Angioedema
Failures
Omalizumab in CU

- Are the responses to omalizumab 150 mg and 300 mg similar?
- How long is needed to see an effect with omalizumab?

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Aspergillus dermatitis and skin disease

Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria


OMALIZUMAB 300 mg faster response than omalizumab 150 mg

Complete Responders Higher in omalizumab 300 mg vs 150 mg


12-16 weeks of omalizumab 300 mg appears sufficient to determine response

Open Label Omalizumab


The XTEND-CIU study: Long-term use of omalizumab in chronic idiopathic urticaria


24-48 weeks omalizumab vs placebo

Probability of Worsening: Omalizumab vs Placebo

Re-Treatment with Omalizumab After 12 weeks of Placebo

Long-term Use of Omalizumab

Outcomes of using omalizumab for more than 1 year in refractory chronic urticaria

Long-term Use of Omalizumab


Urticaria Recurred in Vast Majority with Tapering

Many able to Reduce Frequency to > every 4 weeks, some required more frequent dosing

More frequent Omalizumab Dosing?

- No controlled studies have evaluated more frequent dosing
- Anecdotally, rare patients have a "wear-off" effect
  - More hives days 21-28 post omalizumab
  - Some of these patients may benefit from more frequent dosing

Lack of basophil CD203c-upregulating activity as an immunological marker to predict response to treatment with omalizumab in patients with symptomatic chronic urticaria

Tharmini Palacios, DO,1, Leland Stillman, MD,2, Larry Borish, MD,1,3, and Monica Lawrence, MD

- Retrospective study of 41 pts treated with omalizumab
  - 29 responders
    - 87% absent CD203c activity
  - 12 nonresponders
    - 29% absent CD203c activity
  - Limitations of small sample size and retrospective study

The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change

R. Ertas1 | K. Ozay1 | M. Atsay1 | T. Hasemo2 | M. Maxer2

<table>
<thead>
<tr>
<th>Level of baseline and week 12 IgE, mean ± SD, and percent IgE levels in patients who show complete response (CR) and partial response (PR) to omalizumab treatment</th>
<th>CR (n=20)</th>
<th>PR (n=14)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IgE</td>
<td>517±152</td>
<td>423±145</td>
<td>0.015</td>
</tr>
<tr>
<td>Total IgE</td>
<td>207±56</td>
<td>223±39</td>
<td>0.302</td>
</tr>
<tr>
<td>IgE levels</td>
<td>127±30</td>
<td>128±30</td>
<td>0.946</td>
</tr>
<tr>
<td>IgE levels</td>
<td>92±20</td>
<td>95±20</td>
<td>0.868</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 1: Response of CD patients to omalizumab treatment stratified by baseline IgE level and exceed/10e3 IgE ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgE (kU/L)</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>100–1000</td>
</tr>
<tr>
<td>1000–10000</td>
</tr>
<tr>
<td>10000–100000</td>
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<tr>
<td>100000–1000000</td>
</tr>
</tbody>
</table>

**Ettaas R et al. Allergy. 2018;73(3):705-12.**

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**Vanderbilt University, Allergy, Asthma, and Immunology**

**Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence**


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**Allergy**

**ORIGINAL ARTICLE**

**Experimental Allergy and Immunology**

**Effect of omalizumab on angioedema in H1-antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial**

**Staubach P et al. Allergy. 2016;71(8):1135-44.**
Omalizumab Not Successful 34-44%

When Omalizumab Fails

Other Alternative Agents for Chronic Urticaria

What’s Wrong with Steroids?

Corticosteroid-related toxicity in patients with chronic idiopathic urticaria—chronic spontaneous urticaria

Dennis Lefford, M.D.,1 Michael S. Broder, M.D., M.H.S.,2 Eugenia Antonova, M.S., Ph.D.,3 Theodore A. Omachi, M.D. M.B.A.,7 Eunice Chang, Ph.D.,7 and Allan Laskin, M.D.4

Study of a large health care claims database > 13 million patients

Majority of CU patients used corticosteroids

For every 100 tabs of 10 mg prednisone, there is a 7% increased risk of adverse effects

Alternative Agents in Refractory Chronic Urticaria: Evidence and Considerations on Their Selection and Use

J Allergy Clin Immunol Practice 2013;1:433-40.e1
Evidence for Alternative Therapies in CU

- Overall the evidence for most other alternative therapies is weak
- Few agents have well designed randomized placebo-controlled studies
- Most studies have small number of participants

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J Allergy Clin Immunol Practice 2013;1:433-40.e1

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Anti-Inflammatory Agents for CIU

Dapsone
Sulfasalazine
Hydroxychloroquine
Vitamin D?
Methotrexate
Colchicine
Dapsone

Evidence in Literature: Ib (1 small RCT)

Dose: 50-100 mg daily (I start at 100 mg usually)

Onset of Improvement: 2-6 weeks

Estimated effectiveness frequency: ~50%

Risks:
- Mild anemia expected (Hgb decrease by 10-20%)
- Methemoglobinemia, hepatitis, neuropathy, DRESS rare

Lab monitoring:
- G6PD prior to therapy
- CBC in 2 weeks then monthly CBC with LFT

Cost: $

Remission possible: yes

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Dapsone

Original Article

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


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Dapsone

Itch and overall urticaria severity statistically different dapsone vs placebo
- 3/10 dapsone patients had complete resolution of hives
- Most common adverse effect: decrease in Hgb (mean 13%)

Back to the Case

- Tried 4,000 U Vit D for 2 mos, no effect
- Dapsone 100 mg/d for 6 weeks no effect
- Remains on prednisone 20 mg/d
- Remains frustrated and tearful

Management of Refractory Chronic Urticaria

- Step 1: Other immunomodulatory therapies (IV immunoglobulin, IL-10 receptor antagonist)
- Step 2: Myeloid progenitor cells
- Step 3: Mycophenolate mofetil
- Step 4: Tacrolimus
- Step 5: Rivaroxaban
- Step 6: Cyclosporine

Immunosuppressants for CIU

- Cyclosporine
- Tacrolimus
- Mycophenolate
- Sirolimus

Calcineurin Inhibitors in CU

- Cyclosporine
  - Most evidence with high dose (3-5 mg/kg/d)
  - Rapid effect
  - Low dose 1-2 mg/kg/d better tolerated
  - Slow effect

- Tacrolimus
  - My preferred calcineurin inhibitor
  - 1-2 mg bid (rapid effect)
  - No hirsutism, gingival hyperplasia

Original Article

Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review


Mycophenolate

<table>
<thead>
<tr>
<th>Evidence in Literature</th>
<th>IIb (1 small observational study, few case series)</th>
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</thead>
<tbody>
<tr>
<td>Dose</td>
<td>500-3000 mg twice daily (I start at 500 mg bid and go up to 2000 mg bid with monthly dose increases)</td>
</tr>
<tr>
<td>Onset of Improvement</td>
<td>1-9 weeks</td>
</tr>
<tr>
<td>Estimated effectiveness frequency</td>
<td>30 %</td>
</tr>
<tr>
<td>Risks</td>
<td>GI intolerance (common and dose related)</td>
</tr>
<tr>
<td></td>
<td>Cytopenias, infection (rare), malignancy (very rare)</td>
</tr>
<tr>
<td>Lab monitoring</td>
<td>CBC monthly</td>
</tr>
<tr>
<td>Cost</td>
<td>$$$</td>
</tr>
<tr>
<td>Remission possible</td>
<td>yes</td>
</tr>
</tbody>
</table>

Back to the Case

- Tacrolimus started and titrated up to 5 mg/d over 8 weeks
- Trough tacrolimus level 4 mg/dl
- No improvement in urticaria

Case Finale

- Started on sirolimus and titrated up to 2 mg/d
- Within weeks able to taper prednisone
- Developed lower extremity edema
- Dose reduced to 1 mg/d with improvement in edema and was able to taper off prednisone with complete control of hives
- Able to wean off sirolimus after ~ 1 year of therapy and remains hive free

Treatment of Refractory Chronic Urticaria With Sirolimus

Take Home Point

- Persistence pays off!
- Multiple therapies may be required to find the correct one

68 studies of prevalence of Abs
- Anti-TPO more common
- Thyroid Abs rare in children
- Hypothyroidism and Hashimoto’s more common than hyperthyroidism and Graves
- Conflicting evidence on efficacy of thyroid drugs
- Significant heterogeneity with treatments

Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review


<table>
<thead>
<tr>
<th>Study (year)</th>
<th>IgE and TPO</th>
<th>Hypothyroid</th>
<th>Hyperthyroid</th>
<th>Other Abs</th>
<th>Total treated</th>
<th>Design</th>
<th>Country</th>
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</thead>
<tbody>
<tr>
<td>Kolkhir et al. 2017</td>
<td>14%</td>
<td>45%</td>
<td>20%</td>
<td>0%</td>
<td>70</td>
<td>Cross-sectional</td>
<td>Israel</td>
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<tr>
<td>Kolkhir et al. 2017</td>
<td>15%</td>
<td>40%</td>
<td>25%</td>
<td>0%</td>
<td>75</td>
<td>Cross-sectional</td>
<td>Israel</td>
</tr>
<tr>
<td>Kolkhir et al. 2017</td>
<td>16%</td>
<td>45%</td>
<td>20%</td>
<td>0%</td>
<td>75</td>
<td>Cross-sectional</td>
<td>Israel</td>
</tr>
</tbody>
</table>

Refractory CIU in an 11 yo

11 yo F with > 1 year of daily hives and intermittent angioedema, multiple ED visits
- No clear triggers
- Food avoidance based on skin testing no help
- Current medications
  - Prednisone 15 mg/d x 6 months (gained 80 lbs, now home schooled due to bullying from weight gain)
  - Xolair 300 mg x 4 months
  - Cetirizine 10 bid, Levocetirizine 5 bid, Hydroxyzine 30 qid, Doxepin 30 qhs
  - Famotidine 20 bid

Refractory CIU in an 11 yo

- Labs
  - negative ANA/ENA, TSH, ESR 30, leukocytosis
- Skin biopsy
  - urticaria without vasculitis
- Physical exam
  - BMI 36.5, cushingoid, + striae, numerous blanchable urticaria

Refractory CIU in an 11 yo

- Polypharmacy
  - Stop levocetirizine, cetirizine, taper off hydroxyzine
  - Increase doxepin (monotherapy)
  - Tacrolimus 1 mg bid started
  - Within 2 weeks had complete resolution of hives
  - Prednisone tapered off over 2 months
  - Remains hive free on tacrolimus 1mg/d and Xolair 300 mg and losing weight
Take Home Point

- Don’t be afraid of treating children aggressively with immunosuppressants when appropriate

Current & Future Biologics in CU

How Safe are Alternative Agents?

Original Article:

The Comparative Safety of Multiple Alternative Agents in Refractory Chronic Urticaria Patients

No permanent complications observed.

How Long to Treat?

- Once successful alternative agent found
- Taper off steroids
- Taper off other medications
- Treat with alternative agent until urticaria free for at least 3 months then taper over ~3 months
- Some patients require long term (years) usage
  - Find lowest dose to control CU

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### Table I: Summary of alternative agents used in UC

<table>
<thead>
<tr>
<th>Alternative agent</th>
<th>Ben/Fluc/Ursode</th>
<th>Failed</th>
<th>Partial</th>
<th>Partial cured</th>
<th>Complete cured</th>
<th>Permanent</th>
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<tbody>
<tr>
<td>Benazepril</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Fluclofen</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Ursode</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
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J Allergy Clin Immunol Pract 2017;5:165-70...
Conclusions

- Omalizumab is effective in most patients with refractory CIU, many physical urticarias and angioedema.
- On the whole, the quality of evidence for alternative agents other than omalizumab is weak and limited.
- Nevertheless, despite the absence of high quality evidence, even omalizumab refractory CIU patients still merit therapies that can improve their quality of life.
- The potential risk of a given alternative agent needs to be weighed against the patient’s current quality of life and any adverse effects from current therapy (e.g. oral corticosteroids) for their CIU.

“The art of medicine consists in amusing the patient while nature cures the disease.”

Voltaire (1694-1778)