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

- Gain an understanding of how to appropriately identify failures of Omalizumab therapy.
- Gain an understanding of the use of anti-inflammatory, immunosuppressant and other alternative therapies in refractory urticaria/angioedema.
- Be able to discuss the risks of alternative therapies in refractory Chronic 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
Management of Refractory Chronic Urticaria

Step 1
- Second-generation H1 antihistamines
- Avoid NSAIDs, alcohol, or opiates
- Avoidance of physical triggers

Step 2
- Increase dose of second-generation H1 antihistamine up to 4 times daily recommended dose
- Add first-generation H1 antihistamine (hydroxyzine or doxepin) at bedtime
- Add leukotriene receptor antagonists

Step 3
- Omalizumab 300mg every 4 weeks (titrate dose and/or frequency to effect)
- Anti-inflammatory alternatives (dapsone, hydroxychloroquine, sulfasalazine, or methotrexate)

Step 4
- Immunosuppressants (cyclosporine, mycophenolate, tacrolimus, sirolimus)
- Ultraviolet light therapy

Step 5
- Other immunomodulatory biologics (INF-α inhibitor or IL-1R antagonist)

Step 6
- IVIG, plasmapheresis, etc.

Higher Dose H1 Antihistamines

**SUMMARY STATEMENT 78:** Higher doses of second-generation antihistamines may provide more efficacy but data are limited and conflicting for certain agents. (B)

High Dose Antihistamines in CU

- Cetirizine: conflicting studies
- Fexofenadine: no difference between 60 mg, 120 mg and 240 mg twice a day
- Desloratadine
  - 20 mg > 5 mg in cold urticaria
- Levocetirizine and desloratadine
  - Higher doses better
High Dose Antihistamines in CU


Multiple High Dose Antihistamines

van den Elzen et al. Clin Transl Allergy (2017) 7:4
van den Elzen et al.  
Clin Transl Allergy  (2017) 7:4

Fig. 2  Antihistamine dosages and results. The following dosages were considered as standard dose: levocetirizine 5 mg, desloratadine 5 mg, fexofenadine 180 mg, clemastine 1 mg, hydroxyzine 25 mg, cetirizine 10 mg, loratadine 10 mg, acrivastine 8 mg three times daily.

van den Elzen et al.  
Clin Transl Allergy  (2017) 7:4

Fig. 3  Frequency of side effects, by type of side effect, and maximum dose. The following dosages were considered as standard dose: levocetirizine 5 mg, desloratadine 5 mg, fexofenadine 180 mg, clemastine 1 mg, hydroxyzine 25 mg, cetirizine 10 mg, loratadine 10 mg, acrivastine 8 mg three times daily.
Predicting Response to Antihistamines Based on Histamine Wheal Suppression

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

Large suppression of histamine wheal suggests good response to antihistamines


Step 3

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

Another Case of Chronic Hives

- A 25 yo F notes a > 2 yr history of daily urticaria and episodic angioedema, no physical triggers
- Prior laboratories have been unrevealing
- She has failed high doses of antihistamines including doxepin, hydroxyzine, cetirizine, fexofenadine as well as ranitidine, montelukast and alternative agents including dapsone and hydroxychloroquine
- She does feel that her urticaria flares in her premenstrual phase and will actually improve or go away several days after her period
Could her CU be related to her hormones?

How to test?

How to treat?
Progesterone skin testing

- Skin prick
  - 50 mg/ml
- Intradermal
  - 0.005, 0.05, 0.5 mg/ml diluted in benzyl alcohol or olive oil
- Irritant reactions can be seen with both diluents

**Progestogen Hypersensitivity**

- **Autoimmune Progesterone Dermatitis is old term**
- **New term: Progestogen**
  - Not all are due to progesterone
  - Some from synthetic derivatives
- **Hypersensitivity**
  - Not all dermatitis
  - Not all autoimmune

---

**TABLE V. Summary of patient management and outcomes**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Medical management (N = 13)</th>
<th>Desensitization (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Hormone-based therapies (54%)</td>
<td>Oral protocol (73%) 9 days</td>
</tr>
<tr>
<td></td>
<td>Nonhormonal therapies (62%)</td>
<td>IM protocol (27%) 150 min.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Symptom improvement (92%)</td>
<td>Symptom improvement: dermatologic (88%); asthma/anaphylaxis (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolerating IVF (3 of 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy (2 of 3)</td>
</tr>
</tbody>
</table>

*a*Includes patients co-managed on OCPs.

The 2 anaphylaxis pts tolerated the slow 9 day oral protocol?!

Case Epilogue

- Sera sent to University of Cincinnati with elevation of progesterone-specific IgE
- Referred to gynecology for treatment with GnRH agonist
- She received a dose of 11.25 mg of leuprolide (Lupron) but within a week was found to be pregnant
- Managed CU with antihistamines during pregnancy
- Started on omalizumab 300 mg every month in March 2016 with near complete control of hives
- Treated through a second pregnancy with omalizumab

Original Article

Chronic Idiopathic Urticaria: Systemic Complaints and Their Relationship with Disease and Immune Measures

Judy C. Doong, BS, Kris Chichester, MS, Eric T. Oliver, MD, Lawrence B. Schwartz, MD, PhD, and Sarbjit S. Saini, MD

Baltimore, Md; and Richmond, Va

Number of Systemic Complaints

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?
Diagnosis Testing in CU

**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 etiologic 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-citrullinated protein
  - Cryoglobulin levels
  - Serologic 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)
When Has a Patient Failed Omalizumab?

- Are the responses to omalizumab 150 mg and 300 mg similar?

- How long is needed to see an effect with omalizumab?
Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria

Allen Kaplan, MD,a Marta Ferrer, MD, PhD,b Jonathan A. Bernstein, MD,c Evgeniya Antonova, MS, PhD,d Benjamin Trzaskoma, MS,e Karina Raimundo, MS,f Karin Rosén, MD, PhD,g Theodore A. Omachi, MD, MBA,h Sam Khalil, PhD,a and James L. Zazzali, PhD, MPH,i Charleston, SC, Pamplona, Spain, Cincinnati, Ohio, South San Francisco, Calif, and Basel, Switzerland


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
Longterm Use of Omalizumab


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

Daniel Har, MD; Saurin Patel, MD; and David A. Khan, MD

University of Texas Southwestern Medical Center, Dallas, Texas


Table 1

Baseline patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Steroid use</th>
<th>Length of CI (y)</th>
<th>IGF (mg/dL)</th>
<th>History of angioedema</th>
<th>Failed antihistamines</th>
<th>Failed alternative treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>43</td>
<td>PO daily (20 mg)</td>
<td>2</td>
<td>96</td>
<td>yes</td>
<td>cetirizine, fexofenadine, ranitidine, doxepin, diphenhydramine</td>
<td>dapsone, hydroxychloroquine, tacrolimus, mycophenolate mofetil, azathioprine, IVIG, mycophenolate mofetil, cyclophosphamide</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>60</td>
<td>PO daily (20 mg)</td>
<td>15</td>
<td>73</td>
<td>yes</td>
<td>cetirizine, fexofenadine, ranitidine, doxepin, diphenhydramine</td>
<td>dapsone, hydroxychloroquine, tacrolimus, mycophenolate mofetil, azathioprine, IVIG, mycophenolate mofetil, cyclophosphamide</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>59</td>
<td>PO qd (15 mg)</td>
<td>22</td>
<td>618</td>
<td>no</td>
<td>doxepin, hydroxyzine, fexofenadine</td>
<td>hydroxychloroquine, tacrolimus, mycophenolate, cyclophosphamide</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>40</td>
<td>PO qd (15 mg)</td>
<td>3</td>
<td>87</td>
<td>no</td>
<td>hydroxyzine, doxepin, cetirizine</td>
<td>dapsone, tacrolimus, sulfasalazine</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>56</td>
<td>PO qd (15 mg)</td>
<td>5</td>
<td>2,762</td>
<td>yes</td>
<td>doxepin, fexofenadine, hydroxyzine, leucovorin, lometoline</td>
<td>dapsone, mometoluban</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>28</td>
<td>PO qd (15 mg)</td>
<td>8</td>
<td>412</td>
<td>no</td>
<td>cetirizine, fexofenadine, ranitidine, diphenhydramine</td>
<td>hydroxyzine, tacrolimus, dapsone, tolanecine, oxymetholone</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>40</td>
<td>PO qd (15 mg)</td>
<td>1</td>
<td>10</td>
<td>no</td>
<td>cetirizine, fexofenadine, fexofenadine, diphenhydramine, azathioprine, mycophenolate</td>
<td>mycophenolate</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>20</td>
<td>PO qd (15 mg)</td>
<td>1</td>
<td>94</td>
<td>no</td>
<td>hydroxyzine, fexofenadine, diphenhydramine, cetirizine</td>
<td>mycophenolate</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>45</td>
<td>PO qd (15 mg)</td>
<td>1</td>
<td>10</td>
<td>no</td>
<td>cetirizine, fexofenadine, doxepin, diphenhydramine, leucovorin</td>
<td>hydroxyzine, tacrolimus, UV therapy</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>57</td>
<td>PO qd (15 mg)</td>
<td>13</td>
<td>9</td>
<td>no</td>
<td>cetirizine, loratadine, doxepin</td>
<td>tacrolimus, dapsone, cyclophosphamide</td>
</tr>
</tbody>
</table>

Abbreviations: CI, chronic urticaria; F, female; IVIG, intravenous immunoglobulin; M, male; PO, prednisone; qd, every other day; UV, ultraviolet.

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 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

Retrospective study of 41 pts treated with omalizumab
- 29 responders
  - 87% absent CD203c activity
- 12 nonresponders
  - 25% absent CD203c activity

Limitations of small sample size and retrospective study
### TABLE I. The potential pharmacologic mechanisms of omalizumab in patients with CSU

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding of omalizumab to IgE</td>
<td>↓</td>
</tr>
<tr>
<td>Free IgE concentration in blood and interstitial space</td>
<td>↓</td>
</tr>
<tr>
<td>FcεRI on mast cells and basophils</td>
<td>↓</td>
</tr>
<tr>
<td>IgE-FcεRI engagement</td>
<td>↓</td>
</tr>
<tr>
<td>Potentiating of mast cells</td>
<td>↓</td>
</tr>
<tr>
<td>Secretion of cytokines (without degranulation)</td>
<td>↓</td>
</tr>
<tr>
<td>Mast cell pool</td>
<td>↓</td>
</tr>
<tr>
<td>Immune complexes of IgE-omalizumab</td>
<td>↑</td>
</tr>
<tr>
<td>Trapping of autologous antigens (eg, TPO)</td>
<td>↑</td>
</tr>
<tr>
<td>Trapping of IgE-specific IgG autoantibodies</td>
<td>↑</td>
</tr>
<tr>
<td>Binding of omalizumab to membrane-bound IgE on B lymphocytes</td>
<td>↓</td>
</tr>
<tr>
<td>Continual synthesis of IgE in extended periods</td>
<td>↓</td>
</tr>
<tr>
<td>IgE pool in the immune system</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Overall effects</strong></td>
<td></td>
</tr>
<tr>
<td>Release thresholds for mast cells for various degranulators</td>
<td>↑</td>
</tr>
<tr>
<td>Degranulation of mast cells</td>
<td>↓</td>
</tr>
<tr>
<td>Secretion of mediators, cytokines, and chemokines</td>
<td>↓</td>
</tr>
<tr>
<td>Recruitment of T cells, macrophages, and eosinophils</td>
<td>↓</td>
</tr>
<tr>
<td>Inflammatory manifestation in skin</td>
<td>↓</td>
</tr>
<tr>
<td>Vasopermeability, wheal, edema, itch, and erythema</td>
<td>↓</td>
</tr>
</tbody>
</table>

---

**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 Ledford, M.D.,1 Michael S. Broder, M.D., M.S.H.S.,2 Evgeniya Antonova, M.S., Ph.D.,3 Theodore A. Omachi, M.D, M.B.A.,3 Eunice Chang, Ph.D.,2 and Allan Luskin, 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

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
### Table 1: Selected alternative agents for idiopathic chronic urticaria

<table>
<thead>
<tr>
<th>Alternative agent</th>
<th>Oral dose</th>
<th>Onset of improvement</th>
<th>Estimated effectiveness</th>
<th>Evidence</th>
<th>Risk pregnancy categories</th>
<th>Laboratory monitoring</th>
<th>Cost of treatment</th>
<th>Induction of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone</td>
<td>10 mg daily</td>
<td>2-4 wk</td>
<td>Low</td>
<td>Multiple RCT</td>
<td>Minimal (B)</td>
<td>None</td>
<td>$8</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>500 mg twice daily</td>
<td>&lt;5 wk</td>
<td>Moderate</td>
<td>Case series</td>
<td>Low (C)</td>
<td>Baseline: CBC, LFT, RBC, NO</td>
<td>$</td>
<td>Possible</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>100 mg daily with reductions of dose as tolerated</td>
<td>Up to 6 wk</td>
<td>Moderate</td>
<td>1 RCT</td>
<td>Low (C)</td>
<td>Baseline: CBC, LFT, UNG</td>
<td>$</td>
<td>Unclear</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10-15 mg weekly</td>
<td>1-2 mo</td>
<td>Moderate</td>
<td>Case series</td>
<td>Moderate-high (X)</td>
<td>Baseline: CBC, LFT, UNG, CXR</td>
<td>$</td>
<td>Possible</td>
</tr>
<tr>
<td>Colchicine</td>
<td>0.6 mg twice daily</td>
<td>Unclear</td>
<td>Low</td>
<td>Moderate</td>
<td>Case series</td>
<td>Low (C)</td>
<td>Baseline: LFT, RBC, UNG</td>
<td>$88</td>
</tr>
</tbody>
</table>

### Anti-Inflammatory Agents for CIU

- Dapsone
- Sulfasalazine
- Hydroxychloroquine
- Vitamin D?
- Methotrexate
- Colchicine
# Dapsone

**Evidence in Literature**

<table>
<thead>
<tr>
<th>Evidence in Literature</th>
<th>Ib (1 small RCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>50-100 mg daily (I start at 100 mg usually)</td>
</tr>
<tr>
<td>Onset of Improvement</td>
<td>2-6 weeks</td>
</tr>
<tr>
<td>Estimated effectiveness frequency</td>
<td>~50%</td>
</tr>
<tr>
<td>Risks</td>
<td>Mild anemia expected (Hgb decrease by 10-20%) Methemoglobinemia, hepatitis, neuropathy, DRESS rare</td>
</tr>
<tr>
<td>Lab monitoring</td>
<td>G6PD prior to therapy CBC in 2 weeks then monthly CBC with LFT</td>
</tr>
<tr>
<td>Cost</td>
<td>$</td>
</tr>
<tr>
<td>Remission possible</td>
<td>yes</td>
</tr>
</tbody>
</table>

**Original Article**

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

Dapsone

![Graph showing comparison between Placebo and Dapsone](image)

- Itch and overall urtcaria 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
Second-generation H1 antihistamines
- Avoid NSAIDs, alcohol, or opiates
- Avoidance of physical triggers

Step 2
Increase dose of second-generation H1 antihistamine up to 4 times daily recommended dose
- Add first generation H1 antihistamine (hydroxyzine or desloratadine) at bedtime
- Add leukotriene receptor antagonist

Step 3
Omalizumab 300mg every 4 weeks (titrate dose and/or frequency to effect)
- Anti-inflammatory alternative agent (dapsone, hydroxychloroquine, sulfasalazine, or methotrexate)

Step 4
Immunosuppressant (cyclosporine, mycophenolate, tacrolimus, sirolimus)
- Ultraviolet light therapy

Step 5
Other immunomodulatory biologics
(7NF-α inhibitor or IL-4/IL-13 antagonist)

Step 6
IVIG, plasmapheresis, etc.


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

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
Treatment of Refractory Chronic Urticaria With Sirolimus

Matt Morgan, MD; Allergy, Asthma, and Immunology of North Texas, McKinney; University of Texas Southwestern Division of Allergy and Immunology, Dallas.

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
- Currently weaning down on sirolimus dose slowly

Take Home Point

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

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

- 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 and losing weight
Take Home Point

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

- Anti-IgE monoclonal antibody (omalizumab, ligelizumab)
  - Decreases free IgE levels
  - Downregulates FсεRI expression
  - Prevents IgE from binding to FсεRI
  - IgE
  - Antigen
  - Facilitates IgE from binding to FсεRI

- Rituximab
  - CD20
  - Induces B cells cytotoxicity and decreased antibody production

- Intravenous Immunoglobulin
  - Decreases autoantibody production by B cells

- TNF-α inhibitors
  - Syk Inhibitor (GSK264626)

- Quilizumab
  - Depletion of IgE class-switched B cells

- B cell
  - CD20
  - Induces B cells cytotoxicity and decreased antibody production

- Rituximab
  - Quilizumab

How Safe are Alternative Agents?

Original Article

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

Sharon Seth, MD, and David A. Khan, MD  Dallas, Texas


---

**TABLE I.** Demographic characteristics of 126 patients with CU treated with alternative agents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y) (n = 126)</td>
<td>44 (18-69)</td>
</tr>
<tr>
<td>Sex (n = 126)</td>
<td>77% females, 23% males</td>
</tr>
<tr>
<td>Mean duration (range) of urticaria (mo)</td>
<td>44 (2-444)</td>
</tr>
<tr>
<td>Steroid dependent</td>
<td>78 patients (61%)</td>
</tr>
<tr>
<td>Able to stop or decrease oral steroids while treated with an alternative agent</td>
<td>58 patients (74%)</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>102 patients</td>
</tr>
<tr>
<td>Urticarial vasculitis</td>
<td>6 patients</td>
</tr>
<tr>
<td>Physical urticarias*</td>
<td>28 patients</td>
</tr>
<tr>
<td>Other urticarias†</td>
<td>1 patient</td>
</tr>
</tbody>
</table>

*Delayed pressure urticaria (16 patients), symptomatic dermatographism (9 patients), cholinergic urticaria (1 patient), cold urticaria (1 patient), solar urticaria (1 patient).
†Autoimmune progesterone urticaria (1 patient).
No permanent complications observed.
**TABLE E1.** Combinations of alternative agents used in patients

<table>
<thead>
<tr>
<th>Alternative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. sulfaalazine + tacrolimus</td>
</tr>
<tr>
<td>2. dapsone + hydroxychloroquine; dapsone + sulfaalazine</td>
</tr>
<tr>
<td>3. dapsone + hydroxychloroquine</td>
</tr>
<tr>
<td>4. hydroxychloroquine + mycophenolate</td>
</tr>
<tr>
<td>5. dapsone + sulfaalazine</td>
</tr>
<tr>
<td>6. tacrolimus + hydroxychloroquine</td>
</tr>
<tr>
<td>7. hydroxychloroquine + cyclosporine; hydroxychloroquine + sulfaalazine; hydroxychloroquine + tacrolimus; hydroxychloroquine + mycophenolate; tacrolimus + sulfaalazine; cyclosporine + mycophenolate; hydroxychloroquine + tranexamic + mycophenolate</td>
</tr>
<tr>
<td>8. tacrolimus + omalizumab; tacrolimus + hydroxychloroquine; tacrolimus + sulfaalazine</td>
</tr>
<tr>
<td>9. dapsone + sulfaalazine; sulfaalazine + tacrolimus</td>
</tr>
<tr>
<td>10. omalizumab + cyclosporine</td>
</tr>
<tr>
<td>11. omalizumab + hydroxychloroquine</td>
</tr>
<tr>
<td>12. dapsone + hydroxychloroquine</td>
</tr>
<tr>
<td>13. IVIG + hydroxychloroquine</td>
</tr>
<tr>
<td>14. dapsone + hydroxychloroquine; dapsone + sulfaalazine; dapsone + sulfaalazine + heparin; heparin + stanozolol</td>
</tr>
<tr>
<td>15. omalizumab + mycophenolate</td>
</tr>
<tr>
<td>16. tacrolimus + hydroxychloroquine</td>
</tr>
<tr>
<td>17. dapsone + hydroxychloroquine</td>
</tr>
<tr>
<td>18. dapsone + sulfaalazine</td>
</tr>
<tr>
<td>19. omalizumab + sulfaalazine; omalizumab + cyclosporine</td>
</tr>
<tr>
<td>20. tacrolimus + dapsone; hydroxychloroquine + dapsone; hydroxychloroquine + mycophenolate; hydroxychloroquine + sulfaalazine</td>
</tr>
<tr>
<td>21. dapsone + hydroxychloroquine; omalizumab + mycophenolate</td>
</tr>
<tr>
<td>22. dapsone + hydroxychloroquine</td>
</tr>
<tr>
<td>23. dapsone + hydroxychloroquine</td>
</tr>
<tr>
<td>24. mycophenolate + hydroxychloroquine</td>
</tr>
<tr>
<td>25. dapsone + hydroxychloroquine</td>
</tr>
</tbody>
</table>

---

**TABLE V.** Efficacy of alternative agents

<table>
<thead>
<tr>
<th>Alternative agent</th>
<th>Insufficient duration</th>
<th>Failed</th>
<th>Portal</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>Sulfaalazine</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>2</td>
<td>13</td>
<td>0</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>

J Allergy Clin Immunol Pract 2017;5:165-70..
**How Long to Treat?**

- Once successful alternative agent found
  - Taper off steroids
  - Taper off other medications
- I 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

**Conclusions**

- 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 CU 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 CU
- A logical step wised approach can be used in refractory CU patients to control urticaria and eliminate chronic/frequent steroids
"The art of medicine consists in amusing the patient while nature cures the disease."

Voltaire (1694-1778)