3302: Therapy Options for Patients with Anti-Histamine Resistant Chronic Urticaria

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Disclosure of Off Label Use

• Majority of therapies mentioned are either not FDA-approved for CU or non-FDA approved doses
Overview

• Define “refractory” CU
• Examine the evidence base for CU therapies
• Previous Guidelines – Step algorithms
• 2014 Practice Parameter Update
• Omalizumab phase III trials
What is Refractory CU?

British Society (BSACI) Guidelines on CU

1) Standard dose of minimally-sedating H₁ antihistamine
2) Add H₂ blocker daily
3) Add sedating H1 antihistamine
4) Higher dose of minimally-sedating H₁ antihistamine
5) Add or substitute second-line agent
6) Add or substitute third-line agents

Identification of Triggers, if any

Education and Avoidance of Triggers

*Most of these recommendations are non-FDA-approved in the USA
What is the Evidence Base?
Categories of Evidence

• Ia  Evidence from 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
• IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
Morgan & Khan 2008 – 2^{nd} Line

- LTRA \text{ I} b
- Cyclosporine \text{ I} b
- Hydroxychloroquine \text{ I} b
- Dapsone \text{ II} b
- Mycophenolate \text{ II} b
- Sulfasalazine \text{ III}
- Colchicine \text{ III}
- Prednisone \text{ IV}
Morgan & Khan 2008 – 3rd Line

- Att Androgens  Ib
- Phototherapy  Ib
- Nifedipine  Ib
- Methotrexate  IIb
- IVIG  IIb
- Warfarin/heparin  IIb
- Plasmapheresis  III
- Cyclophosphamide  III
- Gold salts  III

What is the Evidence Base?

• GRADE Approach
  – Category and Quality of Evidence
  – Strength of Recommendation

Atkins et al. *BMC Health Serv Res.* 2004 Dec 22;4(1):38
GRADE Approach

• Separates quality of evidence from strength of recommendations
• Entails criteria for downgrading and upgrading quality of evidence ratings
• Explicitly acknowledges risk- and cost-benefit considerations as well as patient values and preferences

Atkins et al. BMC Health Serv Res. 2004 Dec 22;4(1):38
<table>
<thead>
<tr>
<th>Drug</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation antihistamines (at licensed doses)</td>
<td>High</td>
<td>Strong (+)</td>
</tr>
<tr>
<td>First-generation antihistamines</td>
<td>High</td>
<td>Strong (−)</td>
</tr>
<tr>
<td>Second-generation antihistamines (at higher than licensed doses)</td>
<td>Moderate</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Anti-H2-antihistamines as add-on therapy</td>
<td>Moderate</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Oral corticosteroids (short course)</td>
<td>Low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>Very low</td>
<td>Strong (−)</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists (as add-on therapy)</td>
<td>Low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Anti-inflammatory agents (dapsone, sulfasalazine, hydroxychloroquine, colchicines, mycophenolate mofetil)</td>
<td>Low-very low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Moderate</td>
<td>Weak (+)*</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Very low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Very low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Biologic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Moderate</td>
<td>Weak (+)*</td>
</tr>
<tr>
<td>IVIG</td>
<td>Low</td>
<td>Weak (+)</td>
</tr>
</tbody>
</table>

(+) recommendation for medication; (−), recommendation against medication.

*Although the recommendation is “weak” according to the GRADE approach, it is stronger than in other cases based on the quality of existing evidence.
What do Previous Guidelines Say?

• Step-wise algorithms for therapy
Urticaria 2008

- 3rd International Consensus Meeting on Urticaria
- Workgroup to Create International Guidelines
- Led to 2009 EAACI/GA2LEN/EDF/WAO guidelines

Zuberbier T. *WAO Journal* 2012;5:S1-5
Urticaria 2012

- 4th International Consensus Meeting on Urticaria
- Workgroup to Create International Guidelines
- Using GRADE criteria
- Note that the full guidelines not yet published

Maurer M. J Dtsch Dermatol Ges 2013;epub: doi 10.111/ddg.12194
Urticaria 2008: 4-Step Algorithm

• STEP 1: Second Generation Antihistamine (sgAH)
  ● If symptoms persist after 2 weeks:
• STEP 2: Increase sgAH dose up to 4X
  ● If symptoms persist after 1-4 weeks:
• STEP 3: add LTRA or change sgAH
  ● If symptoms persist after 1-4 weeks:
• STEP 4: Omalizumab, cyclosporine A, H2 antagonist, dapsone

Zuberbier T. WAO Journal 2012;5:S1-5
Urticaria 2012: 3-Step Algorithm

• STEP 1
  – Second Generation Antihistamine (sgAH)
    • If symptoms persist after 2 weeks:
• STEP 2
  – Increase sgAH dose up to 4X
    • If symptoms persist after 1-4 weeks:
• STEP 3
  – Omalizumab, cyclosporine A, LTRA

Maurer M. J Dtsch Dermatol Ges 2013;epub: doi 10.111/ddg.12194
Urticaria Practice Parameter Update 2014

Submitted to JACI – Pending Review

• Chief Editors:
  Jonathan Bernstein, MD, David Lang, MD, David Khan, MD
• Workgroup Contributors:
  Timothy Craig, DO; David Dreyfus, MD; Fred Hsieh, MD;
  Javed Sheikh, MD; David Weldon, MD; and Bruce Zuraw, MD

Recommendations subject to change pending JACI review
Categories of Evidence

- Ia  Evidence from 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 nonexperimental descriptive studies, such as comparative studies
- IV   Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
Strength of Evidence

• A  Directly based on category I evidence
• B  Directly based on category II evidence or extrapolated from category I evidence
• C  Directly based on category III evidence or extrapolated from category I or II evidence
• D  Directly based on category IV evidence or extrapolated from category I, II, or III evidence
• E  Based on consensus of the Joint Task Force on Practice Parameters
Proposed Step-wise Algorithm for Therapy

• 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
Step 1

- Monotherapy with second generation antihistamine [A]
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present [C]
Step 2

• One or more of the following:
  – Dose advancement of 2\textsuperscript{nd} gen AH used in Step 1 [B]
  – Add another 2\textsuperscript{nd} gen AH
  – Add H\textsubscript{2}- antagonist [D]
  – Add leukotriene receptor antagonist [A]
  – Add 1\textsuperscript{st} gen AH to be taken at bedtime [D]
Step 3

• Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated [D]
Definition of Refractory CU

- CU patients who are not adequately controlled on maximal antihistamine therapy (i.e., dose advancement of doxepin, as tolerated) may be considered to have refractory CU. (E)
Step 4

• Add an alternative agent
  – Anti-inflammatory agent (e.g. dapsone, hydroxychloroquine, sulfasalazine [D])
  – Immunosuppressant agent (e.g. cyclosporine [B], mycophenolate or tacrolimus [C], methotrexate [D])
  – Biologic agent
    ● Of agents studied in CU, omalizumab [A]
    ● Others [C]
Other Alternative Agents

- Phototherapy [D]
- Others [D]
  - theophylline, attenuated androgens, anticoagulants, NSAIDs, beta-agonists, cyclophosphamide, gold, plasmapheresis, stanozolol, cromolyn, and nifedipine
Omalizumab Phase III studies
Original Article

Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

Marcus Maurer, M.D., Karin Rosén, M.D., Ph.D., Hsin-Ju Hsieh, Ph.D., Sarbjit Saini, M.D., Clive Grattan, M.D., Ana Gimenéz-Arnau, M.D., Ph.D., Sunil Agarwal, M.D., Ramona Doyle, M.D., Janice Canvin, M.D., Allen Kaplan, M.D., and Thomas Casale, M.D.

N Engl J Med
Volume 368(10):924-935
March 7, 2013
Study Design

• Phase III, randomized, placebo-controlled trial
• CU patients aged 12-75 symptomatic despite licensed doses of sgAH
• 323 patients randomized to 4 arms:
  • Placebo, 75mg, 150mg, 300mg
• 3 doses spaced 4 weeks apart followed by 16 weeks of observation
• Primary efficacy outcome measure: change from baseline in weekly itch severity score (0-21)
Enrollment and Outcomes.

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
  - 50 (34%) Had other reasons
  - 3 (1%) Were rescreened

323 Underwent randomization

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

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

- 83 Were assigned to receive omalizumab, 150 mg
  - 9 (11%) Withdraw from study
    - 1 (1%) Had adverse event
    - 2 (2%) Were lost to follow-up
    - 3 (4%) Withdraw 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%) Withdraw from study
    - 1 (1%) Had adverse event
    - 2 (2%) Were lost to follow-up
    - 3 (4%) Withdraw or were withdrawn by guardian
    - 6 (8%) Had disease progression
  - 67 (85%) Completed study

Figure B: Score for No. of Hives

- Placebo
- Omalizumab, 75 mg
- Omalizumab, 150 mg
- Omalizumab, 300 mg

Week: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28

Mean (±SE) Weekly Score for No. of Hives
Baseline Characteristics of the Patients (Modified Intention-to-Treat Population).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N = 79)</th>
<th>Placebo (N = 82)</th>
<th>Omaluabam (N = 82)</th>
<th>Omaluabam (N = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>43.1±22.3</td>
<td>39.7±15.0</td>
<td>43.0±13.2</td>
<td>44.3±13.7</td>
</tr>
<tr>
<td>Age group — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–17 yr</td>
<td>2 (3)</td>
<td>4 (5)</td>
<td>2 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>18–40 yr</td>
<td>30 (38)</td>
<td>42 (51)</td>
<td>32 (39)</td>
<td>37 (39)</td>
</tr>
<tr>
<td>41–64 yr</td>
<td>44 (56)</td>
<td>31 (38)</td>
<td>43 (53)</td>
<td>39 (49)</td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>3 (4)</td>
<td>5 (6)</td>
<td>3 (4)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>55 (70)</td>
<td>65 (79)</td>
<td>65 (79)</td>
<td>63 (80)</td>
</tr>
<tr>
<td>Race — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>70 (89)</td>
<td>70 (85)</td>
<td>68 (86)</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>6 (8)</td>
<td>16 (20)</td>
<td>6 (7)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Not available</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>6 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>84.3±25.7</td>
<td>82.8±21.2</td>
<td>82.4±20.7</td>
<td>80.4±19.9</td>
</tr>
<tr>
<td>&lt;80 kg — no. (%)</td>
<td>41 (52)</td>
<td>43 (52)</td>
<td>41 (50)</td>
<td>43 (52)</td>
</tr>
<tr>
<td>Body mass index (kg)</td>
<td>30.6±7.7</td>
<td>30.2±7.7</td>
<td>30.0±7.3</td>
<td>29.5±6.3</td>
</tr>
</tbody>
</table>

Clinical

Time since diagnosis of chronic idiopathic urticaria — yr

Mean                                 | 7.6±10.7         | 7.5±7.1          | 7.2±8.9            | 6.1±7.3            |

Median                               | 1.3              | 2.5              | 3.9                | 3.5                |

Previous medications for chronic idiopathic urticaria — no.

In-clinic urticaria                   | 5.3±0.7          | 5.4±0.8          | 5.3±0.7            | 5.3±0.7            |

UAS7†                               | 31.0±6.6         | 30.7±6.9         | 31.4±7.0           | 29.5±6.9           |

Weekly itch severity score††         | 14.0±3.4         | 14.0±3.7         | 14.2±4.1           | 13.7±3.5           |

Weekly score for no. of hives†††††   | 17.0±4.2         | 16.8±4.2         | 17.1±4.1           | 15.8±4.6           |

Overall score on Dermatology Life Quality Index§§§ | 12.6±5.9         | 12.6±5.5         | 13.0±6.1           | 12.7±6.4           |

Presence of angioedema — no. (%)§§§§ | 30 (38)          | 31 (38)          | 30 (38)            | 32 (41)            |

Weekly no. of diphenhydramine tablets (25 mg) as rescue medication### | 7.1±7.7         | 7.8±6.0          | 7.5±7.7            | 6.7±6.8            |

+ Plus-minus values are means ± SD. The modified intention-to-treat population included all patients who had undergone randomization and received at least one dose of a study drug. There were no significant differences among the groups at baseline. Percentages may not total 100 because of rounding.

† Race was self-reported.

‡ The body mass index is the weight in kilograms divided by the square of the height in meters.

§ Data are for 77 patients in the placebo group, 80 in the group assigned to receive 75 mg of omaluzumab, 81 in the group assigned to receive 100 mg of omaluzumab, and 76 in the group assigned to receive 150 mg of omaluzumab.

†† The urticaria activity score (UAS) ranges from 0 to 6, with higher scores indicating greater activity. This value was defined as the largest value among those obtained on screening visits on days 14 and 7 before randomization and on the day 1 visit.

†† The UAS during a 7-day period (UAST) ranges from 0 to 42, with higher scores indicating greater activity and a minimally important difference (MID) of 8.5 to 10.5.

††† These values are based on data that were collected in a patient daily diary in the week before randomization.

††† Daily scores for itch severity were 0 indicating none, 1 indicating mild, 2 indicating moderate, and 3 indicating severe, with weekly totals ranging from 0 to 21 and an MID of 5 or more points.

†††† Daily scores for the number of hives were 0 indicating none, 1 indicating 1 to 2, 2 indicating 3 to 12, and 3 indicating ≥12, and an MID of 0.9 to 1.5 for the weekly average.

§§ The Dermatology Life Quality Index ranges from 0 to 30, with higher scores indicating a worse quality of life and an MID of 2.4 to 3.0.

†††† This value was measured in 78 patients in the placebo group.

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

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N = 79)</th>
<th>75 mg (N = 82)</th>
<th>150 mg (N = 82)</th>
<th>300 mg (N = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itch-severity score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to wk 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-5.1±6.0</td>
<td>-5.9±6.5</td>
<td>-8.1±6.4</td>
<td>-9.8±6.0</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>
<td>-10.5 (-21.0 to 4.5)</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>
<td>-4.8 (-6.5 to -3.1)</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly no. of hive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-5.2±6.6</td>
<td>-7.2±7.0</td>
<td>-9.8±7.3</td>
<td>-12.0±7.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>-2.4 (-19.5 to 5.5)</td>
<td>-6.5 (-21.0 to 8.5)</td>
<td>-10.0 (-21.0 to 3.0)</td>
<td>-13.0 (-21.0 to 10.5)</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>
<td>-7.1 (-9.3 to -4.9)</td>
</tr>
<tr>
<td>Patients with UA57 ≥ at wk 12 — no. (%)</td>
<td>15 (19)</td>
<td>22 (27)</td>
<td>35 (43)</td>
<td>52 (66)</td>
</tr>
<tr>
<td><strong>Overall score on Dermatology Life Quality Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to week 12</td>
<td></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>
<td>-10.2±6.8</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>
<td>-10.0 (-27.0 to 8.0)</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>
<td>-3.8 (-5.9 to -1.7)</td>
</tr>
<tr>
<td>Angioedema-free days from wk 4 through wk 12 — %‡</td>
<td></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>
<td>95.5±14.5</td>
</tr>
<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>
<td>100 (17.9 to 100.0)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Missing scores for week 12 were imputed from baseline weekly scores. NA denotes not applicable.
† Least-squares means were estimated with the use of an analysis of covariance (ANCOVA) model stratified according to the baseline weekly itch-severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg).
‡ P=0.01 for the comparison with placebo.
§ P=0.001 for the comparison with placebo.
¶ The ANCOVA model was stratified according to the baseline weekly number of hives (<median vs. median) and baseline weight (<80 kg vs. ≥80 kg).
‖ The baseline score on the Dermatology Life Quality Index was obtained before administration of a study drug on day 1, and there was no imputation for missing scores for week 12.
¶¶ The ANCOVA model was stratified according to the baseline overall score on the Dermatology Life Quality Index (<median vs. median) and baseline weight (<80 kg vs. ≥80 kg).
†† P=0.02 for the comparison with placebo.
‡‡ Angioedema-free days were defined as the number of days for which the patient responded "no" to the angioedema question in the daily diary divided by the total number of days with a nonmissing diary entry starting at the week 4 visit and ending the day before the week 12 visit. Patients who withdrew before the week 4 visit or who had missing responses for more than 40% of the daily diary entries between the week 4 and week 12 study visits were not included in this analysis.

Table 3. Adverse Events (Safety Population).*

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 79)</th>
<th>75 mg (N = 76)</th>
<th>150 mg (N = 88)</th>
<th>300 mg (N = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>48 (61)</td>
<td>45 (59)</td>
<td>59 (67)</td>
<td>51 (65)</td>
</tr>
<tr>
<td>Any adverse event leading to discontinuation of study drug</td>
<td>0</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Early withdrawal from study due to an adverse event</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Any serious adverse event†</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any adverse event suspected to be caused by study drug</td>
<td>3 (4)</td>
<td>7 (9)</td>
<td>8 (9)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Any severe adverse event‡</td>
<td>7 (9)</td>
<td>4 (5)</td>
<td>5 (6)</td>
<td>6 (8)</td>
</tr>
</tbody>
</table>

* The safety population was defined according to the treatment actually received. A complete list of adverse events is provided in Table S7 in the Supplementary Appendix.
† The nine reported serious adverse events were pneumonia and hemorrhoids in one patient each in the placebo group; angioedema in one patient in the 75-mg group; angioedema and idiopathic urticaria in one patient in the 150-mg group; and melanoma in situ, nephrolithiasis, idiopathic urticaria, tonsillectomy, and melena in one patient each in the 300-mg group. After a review of the hospital discharge summary after the database lock, it was determined that the patient with melena had no anemia; the cause of hospital admission was elective endoscopy for nonanemic melena. The patient underwent upper gastrointestinal endoscopy and colonoscopy, which revealed only diverticulosis with no other potential source of bleeding. Thus, it was determined that this patient had a nonserious event of nonanemic melena rather than a serious adverse event, as initially reported. Additional details about the serious adverse events are provided in Table S8 in the Supplementary Appendix.
‡ A severe adverse event was defined as the occurrence of symptoms causing an inability to perform usual social and functional activities. A complete description of the severe adverse events is provided in the Safety section in the Supplementary Appendix.

Conclusions

• Omalizumab diminished clinical symptoms and signs of chronic idiopathic urticaria in patients who had remained symptomatic despite the use of approved doses of H\textsubscript{1}-antihistamines.

• The frequency of SAEs was low:
  • The rate was higher in the 300 mg group (6%)
  • Placebo group SAE (3%)
  • 75mg and 150mg groups (1%)
Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy

Allen Kaplan, MD, Dennis Ledford, MD, Mark Ashby, PhD, Janice Canvin, MD, FRCPC, James L. Zazzali, PhD, Edward Conner, MD, Joachim Veith, MD, Nikhil Kamath, MD, Petra Staubach, MD, Thilo Jakob, MD, Robert G. Stirling, MB, FRACP, Piotr Kuna, MD, PhD, William Berger, MD, Marcus Maurer, MD and Karin Rosen, MD, PhD

Journal of Allergy and Clinical Immunology
Volume 132, Issue 1, Pages 101-109 (July 2013)
DOI: 10.1016/j.jaci.2013.05.013
Study Design

• Phase III, randomized, placebo-controlled trial
• CU patients aged 12-75 symptomatic despite sgAH at up to 4x licensed dose plus LTRA, H2 antagonist or both.
• 336 patients randomized in a 3:1 ratio to receive:
  • Omalizumab 300mg vs placebo
• 6 doses spaced 4 weeks apart followed by 16 weeks of observation
• Primary objective was to evaluate safety
Fig 1

Screened (n=480)

Excluded (n=144)
- Other/not defined 53 (36.8%)
- Patient missing eDiary entries in 7 days prior to randomization 22 (15.3%)
- Patient not diagnosed as having CIU/CSU refractory to H1-antihistamines, H2-antihistamines and/or LTRAs at the time of randomization 11 (7.6%)

Randomized (n=336)

Placebo (n=84)
- Not treated (n=1)*

Discontinued study drug, n (%) 21 (25.0)
- AE(s) 6 (7.1)
- Physician decision to discontinue treatment 1 (1.2)
- Subject guardian decision to discontinue treatment 5 (6.0)
- Disease progression 9 (10.7)

Completed study drug, n (%) 63 (75.0)

Discontinued before end of study, n (%) 18 (21.4)
- AE(s) 1 (1.2)
- Lost to follow-up 0
- Physician decision to discontinue treatment 1 (1.2)
- Subject guardian decision to discontinue treatment 8 (9.5)
- Disease progression 8 (9.5)

Completed study, n (%) 66 (78.6)

Omalizumab 300 mg (n=252)

Discontinued study drug, n (%) 31 (12.3)
- AE(s) 12 (4.8)
- Physician decision to discontinue treatment 3 (1.2)
- Subject guardian decision to discontinue treatment 5 (2.0)
- Disease progression 11 (4.4)

Completed study drug, n (%) 221 (87.7)

Discontinued before end of study, n (%) 28 (11.1)
- AE(s) 3 (1.2)
- Lost to follow-up 3 (1.2)
- Physician decision to discontinue treatment 1 (0.4)
- Subject guardian decision to discontinue treatment 10 (4.0)
- Disease progression 11 (4.4)

Completed study, n (%) 224 (88.9)
Fig E2
FIG 3. Responder analysis. Patients with a UAS7 of 6 or less (A) or a UAS7 of 0 (B) at week 12.
### Fig E3

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Total n</th>
<th>LSM difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>94</td>
<td>-6.24 (-8.83, -3.65)</td>
</tr>
<tr>
<td>Female</td>
<td>241</td>
<td>-3.92 (-5.69, -2.15)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>11</td>
<td>1.92 (-14.6, 18.47)</td>
</tr>
<tr>
<td>18–64</td>
<td>303</td>
<td>-4.76 (-6.32, -3.20)</td>
</tr>
<tr>
<td>≥65</td>
<td>21</td>
<td>-5.40 (-10.1, -0.66)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>298</td>
<td>-4.71 (-6.20, -3.21)</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>21</td>
<td>-1.92 (-8.40, 4.57)</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>-11.8 (-23.2, -0.51)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>270</td>
<td>-4.27 (-5.92, -2.62)</td>
</tr>
<tr>
<td>non-US</td>
<td>65</td>
<td>-5.40 (-6.56, -2.25)</td>
</tr>
<tr>
<td><strong>Baseline weekly itch severity score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;13</td>
<td>131</td>
<td>-5.78 (-7.43, -4.14)</td>
</tr>
<tr>
<td>≥13</td>
<td>204</td>
<td>-3.64 (-5.78, -1.51)</td>
</tr>
<tr>
<td><strong>Baseline UAS7</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median</td>
<td>164</td>
<td>-5.37 (-7.02, -3.73)</td>
</tr>
<tr>
<td>≥Median</td>
<td>171</td>
<td>-3.35 (-5.80, -0.90)</td>
</tr>
<tr>
<td><strong>Body weight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80 kg</td>
<td>168</td>
<td>-4.09 (-6.30, -1.87)</td>
</tr>
<tr>
<td>≥80 kg</td>
<td>167</td>
<td>-4.88 (-6.78, -2.98)</td>
</tr>
<tr>
<td><strong>Positive CU index test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>103</td>
<td>-2.69 (-5.18, -0.20)</td>
</tr>
<tr>
<td>No</td>
<td>230</td>
<td>-5.31 (-7.08, -3.54)</td>
</tr>
<tr>
<td><strong>Presence of angioedema at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>178</td>
<td>-4.23 (-6.28, -2.18)</td>
</tr>
<tr>
<td>No</td>
<td>157</td>
<td>-5.12 (-7.17, -3.08)</td>
</tr>
<tr>
<td><strong>Previous use of systemic steroids for CIU/CSU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>165</td>
<td>-5.94 (-7.96, -3.91)</td>
</tr>
<tr>
<td>No</td>
<td>170</td>
<td>-3.01 (-5.08, -0.94)</td>
</tr>
<tr>
<td><strong>Level of thyroperoxidase antibody at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;34.99 U/mL)</td>
<td>53</td>
<td>-5.12 (-8.33, -1.91)</td>
</tr>
<tr>
<td>Normal (≤34.99 U/mL)</td>
<td>277</td>
<td>-4.28 (-5.89, -2.66)</td>
</tr>
<tr>
<td><strong>Duration of disease prior to baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>59</td>
<td>-2.86 (-7.39, 1.87)</td>
</tr>
<tr>
<td>2–10 years</td>
<td>146</td>
<td>-5.61 (-7.72, -3.50)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>79</td>
<td>-3.56 (-6.45, -0.67)</td>
</tr>
<tr>
<td><strong>Previous number of CIU/CSU medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>0.14 (-4.95, 5.23)</td>
</tr>
<tr>
<td>3–5</td>
<td>126</td>
<td>-2.97 (-5.51, -0.43)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>186</td>
<td>-5.88 (-7.77, -3.98)</td>
</tr>
<tr>
<td><strong>Previous use of CIU/CSU therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&lt;sub&gt;1&lt;/sub&gt;-antihistamines + H&lt;sub&gt;2&lt;/sub&gt;-antihistamines only</td>
<td>186</td>
<td>-4.67 (-6.64, -2.71)</td>
</tr>
<tr>
<td>H&lt;sub&gt;1&lt;/sub&gt;-antihistamines + H&lt;sub&gt;2&lt;/sub&gt;-antihistamines + LTRAs only</td>
<td>89</td>
<td>-3.83 (-6.57, -1.10)</td>
</tr>
<tr>
<td>H&lt;sub&gt;1&lt;/sub&gt;-antihistamines + LTRAs only</td>
<td>47</td>
<td>-5.79 (-10.2, -1.34)</td>
</tr>
<tr>
<td>Other CIU/CSU medication combinations</td>
<td>13</td>
<td>NE</td>
</tr>
</tbody>
</table>

Source: Journal of Allergy and Clinical Immunology 2013; 132:101-109 (DOI:10.1016/j.jaci.2013.05.013)

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Conclusions

• Omalizumab was well tolerated and reduced the signs and symptoms of CU in patients who had remained symptomatic despite the use of sgAH at doses of up to 4X the approved dose, plus LTRA, H2 blocker or both.

• The frequency of AEs overall was similar between drug and placebo

• SAEs in omalizumab group: (7.1%)

• SAEs in placebo group: (6%)
Urticaria Practice Parameter Update 2014

Submitted to JACI – Pending Review

- Chief Editors:
  Jonathan Bernstein, MD, David Lang, MD, David Khan, MD
- Workgroup Contributors:
  Timothy Craig, DO; David Dreyfus, MD; Fred Hsieh, MD;
  Javed Sheikh, MD; David Weldon, MD; and Bruce Zuraw, MD

Recommendations subject to change pending JACI review
Cyclosporine evidence rigorously evaluated using GRADE criteria

“Cyclosporine is the only agent that has been studied in several randomized controlled trials”

“The quality of evidence supporting use of cyclosporine for refractory chronic urticaria/angioedema is low”

“…methodologic shortcomings which lead to a weak recommendation for the use of cyclosporine”
Thyroxine

• “There is a lack of high quality evidence demonstrating the efficacy of thyroid hormone supplementation for euthyroid CU patients with evidence of thyroid autoimmunity. For this reason, clinicians should be flexible in their decision making regarding the appropriateness of prescribing thyroid hormone in this setting” [C]
Systemic Corticosteroids

- Systemic corticosteroids are frequently used for refractory CU patients, but no controlled studies have demonstrated efficacy. In some patients, short-term use (e.g. 1-3 weeks duration) may be required to gain control of their disease until other therapies can achieve control. Because of the risk of adverse effects with systemic corticosteroids, long-term use for treatment of CU patients should be avoided as much as possible. (D)
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Recommendations subject to change pending JACI review
3302: Therapy Options for Patients with Anti-Histamine Resistant Chronic Urticaria

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