ORTICARIA AUTOIMMUNE E TIROIDE

Alessandro Farsi
U.O.S.D. Allergologia e Immunologia Clinica
Azienda USL4, Prato
Chronic Urticaria

- Prevalence estimated to be between 0.6-5%
- No clear prevalence data in the U.S.
- More common in middle-age (not 1000 AD)
- More common in females
- Generally has prolonged duration > 1 yr in 70%
  1 to 5 years in about 9%
  > 5 yrs in 11-14%
- Approximately 40% of patients with chronic urticaria have angioedema

<table>
<thead>
<tr>
<th>Score</th>
<th>Wheals</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild (&lt;20 wheals/24 h)</td>
<td>Mild (present but not annoying or troublesome)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate (20–50 wheals/24 h)</td>
<td>Moderate (troublesome but does not interfere with normal daily activity or sleep)</td>
</tr>
<tr>
<td>3</td>
<td>Intense (&gt;50 wheals/24 h or large confluent areas of wheals)</td>
<td>Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)</td>
</tr>
</tbody>
</table>

Sum of score: 0–6
Classification of chronic urticaria

- Urticarial vasculitis
- Physical urticaria
- Ordinary chronic urticaria
- Contact urticaria
- Schnitzler's syndrome
- Autoimmune urticaria
- Chronic idiopathic/spontaneous urticaria (CIU or CSU)
**Recommended Diagnostic Tests In Chronic Urticaria (EAACI)**

**Routine Diagnostic Tests (recommended)**
- Differential blood count and ESR or CRP
- Omission of suspected drugs (e.g. NSAID)

**Extended Diagnostic Program /Tests (suggested) if indicated**
- Infectious diseases (e.g. H pylori)
- Type I allergy (e.g. latex)
- Functional autoantibodies, anti-FcεR test or “CUI”
- Thyroid hormones/autoantibodies
- Physical urticaria tests
- Pseudoallergen-free diet for 3 wks
- Autologous serum skin test
- Lesional skin biopsy

Allergy 2009; 64: 1417-1426
"Psuedoallergens" = substances that induce intolerance reactions: food additives, vasoactive substances, fruits, vegetables, spices.

Days 1-7
- Usual foods

Days 8-10
- rice, potatoes, bread, butter, salt, olive oil, coffee, tea

Days 11-31
- pseudoallergen free

An association of CIU with thyroid autoimmunity

Antigen-antibodies reactions bring about leukocyte degranulations

Autoantibody Induced Chronic Urticaria
Hide M, et.al. NEJM 1993; 328: 1599-604

• 26 patients with CIU were skin tested intradermally to autologous serum (0.05 cc) which elicited a wheal/flare response suggesting an autoantibody to FcεRIα subunit
• Incubation of basophils isolated from a non-atopic donor (low serum IgE) with serum from these patients demonstrated an increase in histamine release
• Passive sensitization of basophils with myeloma IgE and pretreatment with IgG fractions containing sFcεRIα abolished histamine release; basophils, treated with lactic acid to dissociate IgE, and then passively sensitized to serum from patients with autoantibodies to FcεRI, resulted in enhanced histamine release

**Conclusion:** Proposed mechanism of autoimmune induced chronic urticaria is due to cross-linking of IgE receptors by an IgG antibody to FcεRIα resulting in release of bioactive mediators such as histamine
Autoantibody Associated Chronic Urticaria

Approximately 30-50% of patients with CU produce specific IgG antibodies against FcεRIα subunit component of the high affinity IgE receptor.

*IgG antibody to α-subunit of FcERI (35-40%); IgG antibody to α-subunit of IgE (5-10%)
TEST INTRADERMICO CON SIERO AUTOLOGO

- Sangue coagulato a temperatura ambiente per 30'
- Plasma separato per centrifugazione a 500 giri per 15 minuti
- Iniezione intradermica di 50 μL (=0,05 ml)
- Lettura a 30 minuti
- Positivo se pomfo (+alone eritematoso) >1,5 mm del controllo con fisiologica
Toubi E et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients

*Allergy* 2004;59:869-873
The autologous serum skin test in the follow-up of patients with chronic urticaria.

_R Fusari, C. Colangelo, F. Bonifazi, L. Antonicelli_

Allergy 2005: 60: 256–258

82 p. (60 F)  
39 aa ± 15  
ASST+ 46,6%  
HT+CU 29,3%  
ASST+:  
- nel 62% HT pos  
- nel 39% HT neg  
Dopo 1 anno:  
28/34 dei p. ASST+ erano asintomatici  

[Graph showing distribution of Chronic autoimmune urticaria and Chronic urticaria and Hashimoto thyroiditis]
Basophil and mast cell assays for functional autoantibodies in CU

Basophil histamine release assay (BHRA) among patients with CU:
- 32.5% BHRA+
- 25% ASST+/BHRA+
- 49.5% ASST-/BHRA-
- 15.8% ASST+/BHRA-
- 4.1% ASST-/BHRA+

Basophil Activation marker expression (CD 63 and CD203c)

Allergy 2013; 68: 27-36
Odds Ratio of different autoimmune biomarkers of a refractory outcome in CSU

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>OR</th>
<th>P</th>
<th>Cost US$/Euro</th>
</tr>
</thead>
<tbody>
<tr>
<td>CU Index</td>
<td>4.5</td>
<td>.005</td>
<td>436/337</td>
</tr>
<tr>
<td>ANA+ATG+ATPO</td>
<td>3.1</td>
<td>.01</td>
<td>330/255</td>
</tr>
<tr>
<td>ANA</td>
<td>2.3</td>
<td>.04</td>
<td>84/65</td>
</tr>
</tbody>
</table>

Chronic urticaria and autoimmunity: Associations found in a large population study
Confino-Cohen, JACI 2012;129:1307

✔ 12,778 patients with CU during 17 years in a large health maintenance organization.

✔ A control group of 10,714 patients who had no CU.

In patients with CU OR for

- Hypothyroidism: 17.3
- Hyperthyroidism: 28.8
- Rheumatoid arthritis: 13.2
Serum thyroid autoantibodies in patients with idiopathic either acute or chronic urticaria

S. Gangemi1, S. Saita1, G. Lombardo1, M. Patelli1, and S. Benvenga2

1Operative Unit and School Allergology and Clinical Immunology, Department of Pathology and Department of Endocrinology, University of Messina, Messina, Italy

ABSTRACT. In Italy, only one study was conducted on the detection of serum thyroid autoantibodies (ATA) in patients with urticaria. This northern-Italy study reported a 23% rate of ATA positivity in 52 patients with chronic idiopathic urticaria (CIU). During the years 1998-2006, 688 patients with urticaria were hospitalized at our Division of Allergy and Clinical Immunology. Thyroglobulin and thyroperoxidase autoantibodies (TgAb and TPOAb) were assayed at admission in 144/688 patients. Of the 144 patients (mean age: 42.2±15.8 yr, range 17-84), 96 (67% women and 23 men) had an history of CIU (CIU group) and 48 (44 women and 5 men) did not (acute urticaria group or AUB). Of the 144 patients, 3 (2.5%) tested positive for at least one ATA: 31 with CIU (32.6%) and 6 with AUB (12.2%, χ2=7.033, p=0.008). Positivity for TPOAb or TgAb was 30/37 (81.1%) or 17/37 (45.9%), 10/37 (27.0%). Pre-hospitalization duration of CIU was longer in the 31 ATA positive patients compared to the 64 ATA negative patients (207.2±23.4 vs 81.6±106.3 weeks, p<0.015). Pre-hospitalization duration of CIU correlated positively with the log10 transformed serum concentration of TgAb in the 25 CIU patients who tested TgAb positive (r=0.42, p=0.039). We conclude that our rate of 31/95 (32.6%) positivity for at least one type of ATA in CIU is greater than that of 6 representative international studies published between the years 2000 and 2006 (111/408 or 22.7%, range 15-29%, χ2=6.894, p=0.027) (J. Endocrinol. Invest. 32: 107-110, 2009). ©2009, Editrice Kurtis

INTRODUCTION

Chronic urticaria (CIU) is the daily or almost daily occurrence of wheals for at least 6 weeks. CIU is defined idiopathic (CIU) when signs of vascule disease and no causative drugs, foods or physical factors can be identified. In 10 to 40% of CIU patients antibodies against the high affinity receptor for IgE (anti-FcεRI, AUB) have been detected. The association between CIU and Hashimoto's thyroiditis (HT) was first described in 1963. In 17 of 140 consecutive cases of CIU (12.1%), Lezcaff et al. showed biochemical evidence of thyroid autoimmunity based on serum titers of thyroid microsomal autoantibodies (TMAb) ≥1:1600. This rate was 2-fold greater than the 5.6% rate found in 477 controls. In a subsequent study on 624 patients with CIU and angioedema, the rate of positivity for TMAb and/or thyroglobulin autoantibodies (TgAb) was 14.4% (5). The mechanism for the association between CIU and thyroid autoimmunity remains unclear. It has been hypothesized that a cross-linking of the mast cell IgE receptors induced by thyroid autoantibodies (ATA) might cause mast cells to release histamine. Here we report the magnitude of the association between CIU and thyroid autoimmunity in consecutive patients hospitalized for CIU at the local University hospital, and the relationship between this association and a number of variables.

MATERIALS AND METHODS

Patients

As shown in Figure 1, our study comprises 688 consecutive patients hospitalized at our Division of Allergy and Clinical Immunology for idiopathic urticaria over 9 yr (January 1, 1998 through December 31, 2006). Of these 688 patients (435 females and 253 males), only 144 underwent the screening for thyroid autoimmunity, including 96 (67% women and 23 men) with a history of CIU (CIU group) and 48 (44 women and 5 men) without a CIU history (AUB group).

688 patients hospitalized at the Division of Allergy and Clinical Immunology from 01/01/1998 to 01/12/2006 and diagnosed with urticaria

Assay for serum ATA
(TgAb, TPOAb)

No no=544

Yes no=144

M: 29

F: 116

CIU

no=95

age: 42.2±15.8

M: 53

F: 42

AUB

no=69

age: 41.8±16.0

M: 5

F: 44

Fig. 1 - Characteristics of the patients screened for serum thyroid autoantibodies (ATA). TgAb: thyroglobulin autoantibodies; TPOAb: thyroperoxidase autoantibodies; CIU: chronic idiopathic urticaria; AUB: acute urticaria; M: males; F: females.

The association between thyroid autoimmunity and chronic urticaria (CIU) has long been recognized as significant. The prevalence of anti-thyroid antibodies (ATA) has been estimated as 12 to 29%. However, most studies have suggested that these auto-antibodies are not a direct causative agent in CIU. In some patients, ATAs are associated with the presence of anti-thyroglobulin E receptor antibodies. It appears more likely that these antibodies are associated, parallel, auto-immune events. The effects of hormonal treatment on clinical symptoms of CIU are controversial. They must be evaluated by controlled trials.

Abstract

Chronic urticaria and thyroid autoimmunity: a review

The association between thyroid autoimmunity and chronic urticaria (CIU) has long been recognized as significant. The prevalence of anti-thyroid antibodies (ATA) has been estimated as 12 to 29%. However, most studies have suggested that these auto-antibodies are not a direct causative agent in CIU. In some patients, ATAs are associated with the presence of anti-thyroglobulin E receptor antibodies. It appears more likely that these antibodies are associated, parallel, autoimmune events. The effects of hormonal treatment on clinical symptoms of CIU are controversial. They must be evaluated by controlled trials.

Index Entries

Chronic urticaria, thyroid autoimmunity, auto-immunity.
The prevalence of thyroid autoimmunity in patients with urticaria: systematic review and meta-analysis

Xi-Feng Pan · Jian-Qiu Gu · Zhong-Yan Shun

Received: 26 May 2014/Accepted: 12 July 2014 © Springer Science+Business Media New York 2014

Abstract Thyroid autoimmunity is the most common organ-specific autoimmune disorder, which is characterized by the production of thyroid autoantibodies and lymphocytic infiltration into the thyroid. The majority cases of chronic urticaria have unknown (idiopathic) causes, with about 30–40 % possibly having an autoimmune substrate. Considering that autoimmune factors may be the common features of both thyroid autoimmunity and urticaria, it is likely that both entities may coexist within the same patient. A number of studies have investigated the association between thyroid autoimmunity and urticaria. However, most of these studies are relatively small sample size, the power achieved in those studies was not sufficient to detect whether there is an association between urticaria and thyroid autoimmunity. The aim of this study is to combine primary data from all relevant studies to produce reliable estimates of the associations between thyroid autoantibodies and urticaria. Literature databases were searched including Medline, Embase, Web of Science, Chinese Wanfang, and CBM databases from January 1980 to December 2013. A total of 14293 urticaria cases and 12399 non-urticaria controls were included in this study. From these data, the odds ratio (OR) with 95 % confidence interval (95 % CI) was calculated. The meta-analysis results showed that the prevalence of positive thyroid autoantibodies in patients with urticaria was higher than non-urticaria controls (TgAb: OR: 6.55, 95 % CI 3.19–13.42, P < 0.00001, I² = 67 %; TMAb: OR: 4.51, 95 % CI 2.74–7.33, P < 0.00001, I² = 47 %; TPOAb: OR 8.71, 95 % CI 6.89–11.01, P < 0.00001, I² = 20 %, respectively). The results of this meta-analysis suggested that patients with urticaria were more likely to have thyroid autoimmunity than the control groups.

Keywords Thyroid autoimmunity · Urticaria · Meta-analysis

Introduction Thyroid autoimmunity is the most prevalent autoimmune disorder affecting up to 5 % of the general population [1, 2]. The clinical presentation varies from hyperthyroidism in Graves’ disease to hypothyroidism in Hashimoto’s thyroiditis. Thyroid autoimmunity is characterized by the production of thyroid autoantibodies and lymphocytic infiltration into the thyroid. The laboratory diagnosis of thyroid autoimmunity by evaluating the titers of thyroid autoantibodies is necessary. While the exact etiology of thyroid autoimmunity is not known, the interaction between genetic susceptibility and environmental factors appears to be of fundamental importance to initiate the process of thyroid autoimmunity [3, 4].

Urticaria is a frequent disease, with complex etiopathogenesis, raising important problems in clinical practice. In general population about 15–20 % of subjects have suffered from one episode of urticaria–angioidema syndrome in their life. Urticaria is frequently caused by allergic reactions, but there are also many non-allergic causes. The majority cases of chronic urticaria have unknown (idiopathic) causes, with about 30–40 % possibly having an autoimmune substrate [5, 6]. Since autoimmune factors play an important role in the pathogenesis of urticaria,

Descritto il caso di un bambino di 9 anni affetto da CU e anti-TPO positivi che ha ottenuto una prolungata remissione a seguito di terapia con tiroxina.

Sono stati descritti, tuttavia, casi analoghi che non hanno tratto vantaggio dalla terapia ormonale.
High prevalence of autoimmune urticaria in children with chronic urticaria

Luigia Brunetti, MD,^a^ Ruggiero Francavilla, MD, PhD,^a^ Vito L. Miniello, MD,^a^ Michael H. Platzer, MSc,^b^ Domenica Rizzi, MD,^a^ Maria Letizia Lospalluti, MD,^a^ Lars K. Poulsen, PhD,^b^ Lucio Armenio, MD, PhD,^a^ and Per Stahl Skov, MD, PhD^b^

Bari, Italy, and Copenhagen, Denmark
Il concetto che l'orticaria cronica (CU) sia spesso di origine autoimmune è supportato da:

a)associazione di CU con una varietà di malattie autoimmuni (tireopatie autoimmuni, artrite reumatoide giovanile, diabete mellito, celiachia)
b)pazienti con autoanticorpi che non rispondono agli antiistaminici possono trarre beneficio da terapie quali plasmaferesi, immunoglobuline EV, ciclosporina
Celiac Disease Associated With Familial Chronic Urticaria and Thyroid Autoimmunity in a Child
Arie Levine, Ilan Dalal and Yoram Bujanover
*Pediatrics* 1999;104:25-

In alcuni pazienti anticorpi antitiroide sono stati trovati alcuni anni dopo l’esordio dell’orticaria

I dati della letteratura indicano che la tireopatia autoimmune associata alla CU è un processo in evoluzione che si può manifestare prima, durante o dopo la comparsa dell’orticaria

Anche i soggetti eutiroidei con anti-TPO positivi hanno un rilevante rischio di progressione verso l’ipotiroidismo

E’ raccomandata, pertanto, una rivalutazione annuale della funzione tiroidea nei soggetti con CU.
Chronic Urticaria and Thyroid Autoantibodies

Thyroid auto-antibodies are frequently identified in patients with CU. The clinical relevance of these tests for patients with CU has not been established. For this reason, these tests are not routinely indicated.

- Uncertain whether identification of autoantibodies represent a parallel abnormality which reflects an underlying autoimmune process or is functionally related to chronic urticaria

- Involvement of common genetic factors (HLA-DR4) in pathogenesis rather than shared epitope cross-specificity between antithyroid and anti-FcεRIα antibodies
AUTOIMMUNE URTICARIA:
IS IT A REAL ENTITY?

Revised Witebsky’s postulates
(Rose NR, Bona C. Immunology Today 1993; 14: 426-430)

1) Direct evidence from transfer of pathogenetic antibodies or Tcell

2) Indirect evidence based on reproduction of the disease under question in experimental models

3) Circumstantial evidence for clinical practice
PROPOSED GOLD STANDARD FOR DIAGNOSIS OF ACU

A) A positive bioassay (BHRA or basophil activation marker expression) to demonstrate functionality *in vitro* AND

B) Positive autoreactivity (by means of a positive ASST) to demonstrate relevance *in vivo* to MC degranulation and vasopermeability AND

C) A positive immunoassay for specific IgG autoantibodies against FceRIα and/or anti-IgE (WB or ELISA) to demonstrate antibody specificity

Allergy. 2013; 68: 27-36
First line:
Modern second generation antihistamines

If symptoms persist after 2 weeks

Second line:
Increase dosage up to fourfold of modern second generation antihistamines

If symptoms persist after 1–4 further weeks

Third line:
Add on to second line: Omalizumab or Ciclosporin A or Montelukast
Short course (max 10 days) of corticosteroids may also be used at all times if exacerbations demand this
### STEP 1
Monotherapy with second generation antihistamine
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.

### STEP 2
One or more of the following:
- Dose advancement of 2nd generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add H2- antagonist
- Add leukotriene receptor antagonist
- Add 1st generation antihistamine to be taken at bedtime

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

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

- 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
Treatment of chronic autoimmune urticaria with omalizumab

Allen P. Kaplan, MD, Kusumam Joseph, PhD, Robert J. Maykut, MD, Gregory P. Geba, MD, MPH, and Robert K. Zeldin, MD Charleston, SC, and East Hanover, NJ
Methods

• Twelve patients with CAU, identified by basophil histamine release assay and autologous skin test, with persistent symptoms for at least 6 weeks despite antihistamines.

• Treated with placebo for 4 weeks followed by omalizumab (≥0.016mg/kg/IU mL-1 IgE per month) every 2 or 4 weeks for 16 weeks.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Duration of symptoms (continuous)</th>
<th>Total serum IgE (IU/mL)</th>
<th>Thyroid antibodies</th>
<th>Baseline UAS (0-9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>F</td>
<td>11 mo</td>
<td>102</td>
<td>Negative</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>F</td>
<td>30 y</td>
<td>81</td>
<td>(*) Negative</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>2.5 y</td>
<td>39</td>
<td>(+) Antiperoxidase (824)</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>M</td>
<td>3 y</td>
<td>59</td>
<td>Negative</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>M</td>
<td>12 y</td>
<td>10</td>
<td>Negative</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>M</td>
<td>1 y</td>
<td>18</td>
<td>(+) Antiperoxidase (54)</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>F</td>
<td>6 mo</td>
<td>2</td>
<td>Negative</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>F</td>
<td>7 wk</td>
<td>22</td>
<td>(+) Antiperoxidase (250)</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>F</td>
<td>18 y</td>
<td>44</td>
<td>(+) Antiperoxidase (50)</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>F</td>
<td>7.5 y</td>
<td>69</td>
<td>(+) Antithyroglobulin (41)</td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td>52</td>
<td>F</td>
<td>3 mo</td>
<td>26</td>
<td>Negative</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>59</td>
<td>F</td>
<td>4 mo</td>
<td>4</td>
<td>Negative</td>
<td>9</td>
</tr>
</tbody>
</table>

* Female; *M* male.

(*) History of Hashimoto thyroiditis, although autoantibodies were negative.

(+) Positive. titer shown in parentheses.
FIG 1. UASs of 12 patients with chronic autoimmune urticaria treated with omalizumab for 16 weeks. A, Means and SDs of UASs of all 12 patients. Statistically significant decrements in symptom scores were observed at weeks 4, 8, 12, and 16. B, The response of 4 patients with complete resolution of symptoms. C, The response of 4 patients who had a partial improvement in symptoms. D, Single patient with no response.

FIG 2. The use of hydroxyzine by 12 patients with chronic urticaria treated with omalizumab. Hydroxyzine was taken on an as-needed basis for a 20-week period by the study patients. A, Means and SDs of the use of hydroxyzine by all 12 patients. B, Patients with a marked response. C, Patients with partial response showing progressively less use of drug in most instances. D, The patient with no response.
What happens after omalizumab therapy was stopped?

• Kaplan et al investigated the post-treatment clinical course over the 2 years following discontinuation of omalizumab (4 month trial)

• Of the 7 complete responders, 5 had no recurrence, one experienced a mild exacerbation 6 months later that spontaneously resolved, and one experienced intermittent urticaria treated with as-needed hydroxyzine.
What happens after omalizumab therapy was stopped?

• Of the 4 patients with a partial response:
  • One had mild urticaria for 6 months which then worsened requiring prednisone and diphenhydramine for 1 year and is now treated with cetirizine
  • Two have had continuous mild urticaria for 2 years treated with cetirizine, and hydroxyzine respectively
  • One worsened immediately after omalizumab was stopped
    – Required cyclosporine therapy for 1 1/2 years and is now treated with cetirizine
Original article

Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase

Marcus Maurer, MD, Sabine Altrichter, MD, Thomas Bieber, MD, Tilo Biedermann, MD, Matthias Bräutigam, PhD, Stefan Seyfried, PhD, Randolf Brehler, MD, Jürgen Grabbe, MD, Nicolas Hunzelmann, MD, Thilo Jakob, MD, Andreas Jung, MD, Jörg Kleine-Tebbe, MD, Martin Mempel, MD, Michael Meurer, MD, Kristian Reich, MD, Franziska Ruëff, MD, Kaushik Sengupta, BDS, MScD, Christian Sieder, MSc, Jan C. Simon, MD, Bettina Wedi, MD, Torsten Zuberbier, MD, Vera Mahler, MD, and Petra Staubach, MD

Berlin, Bonn, Tübingen, Nürnberg, Münster, Lübeck, Köln, Freiburg, Gießen, Göttingen, Munich, Dresden, Hamburg, Leipzig, Hannover, Erlangen, and Mainz, Germany, Basel, Switzerland, and Hyderabad, India
Study

- In this multicenter, randomized, double-blind, placebo-controlled study patients with CU (male/female, 18-70 years of age) with IgE autoantibodies against TPO who had persistent symptoms (wheals and pruritus) despite standard antihistamine therapy.

- Randomized to receive either omalizumab (75-375 mg, dose determined by using the approved asthma dosing table) or placebo subcutaneously once every 2 or 4 weeks for 24 weeks.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Omalizumab (n = 27)</th>
<th>Placebo (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD (range)</td>
<td>39.1 ± 9.0 (24-57)</td>
<td>42.3 ± 15.0 (20-69)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (29.6)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (70.4)</td>
<td>19 (86.4)</td>
</tr>
<tr>
<td>Race, no. (%) white</td>
<td>27 (100.0)</td>
<td>22 (100.0)</td>
</tr>
<tr>
<td>Height (cm), mean ± SD (range)</td>
<td>171.0 ± 7.2 (160-187)</td>
<td>164.1 ± 6.6 (149-176)</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD (range)</td>
<td>81.9 ± 20.2 (56-130)</td>
<td>71.2 ± 12.4 (51-92)</td>
</tr>
<tr>
<td>IgE–anti-TPO (IU/mL), mean ± SD</td>
<td>7.3 ± 4.6</td>
<td>6.2 ± 3.7</td>
</tr>
<tr>
<td>Total IgE (IU/mL), mean ± SD</td>
<td>211 ± 158</td>
<td>181 ± 136</td>
</tr>
</tbody>
</table>
FIG 2. A. Change in UASs after 24 weeks of treatment. Difference between omalizumab and placebo = -9.9 (95% CI, 2.7-17.1). Population for analysis: intention-to-treat population. Analysis of covariance model: variables = baseline, center, and treatment. Least squares mean after adjusting the covariates, such as center, baseline value, and treatment group. B. Mean daily UAS. The standardized UAS over 24 weeks was significantly lower for omalizumab than placebo (P = .0002). Population for analysis: intention-to-treat population.

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 Giménez-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.
Study Design - Asteria II

Screening Period  
2 Weeks

Treatment Period  
12 Weeks

Follow-Up Period  
16 Weeks

Day -14  
Day 1  
Week 4  
Week 8  
Week 12  
Week 16  
Week 20  
Week 24  
Week 28

Week 12: primary endpoint assessment

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

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

DPH=diphenhydramine
**Primary Endpoint: Change From Baseline In Weekly Itch-Severity Score At Week 12 (mITT)**

- Significant improvements in weekly ISS with omalizumab 150 mg and 300 mg doses vs. placebo

<table>
<thead>
<tr>
<th>Change from baseline in weekly ISS at Week 12</th>
<th>Placebo (N=79)</th>
<th>Omalizumab 75 mg (N=82)</th>
<th>Omalizumab 150 mg (N=82)</th>
<th>Omalizumab 300 mg (N=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>−5.1 (5.6)</td>
<td>−5.9 (6.5)</td>
<td>−8.1 (6.4)</td>
<td>−9.8 (6.0)</td>
</tr>
<tr>
<td>LSM treatment difference vs. placebo (95% CI)</td>
<td>−0.7 (−2.5, 1.2)</td>
<td>−3.0 (−4.9, −1.2)</td>
<td>−4.8 (−6.5, −3.1)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.4637</td>
<td>0.0011</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence interval; ISS=Itch-Severity Score; LSM=least squares mean; mITT=modified intention-to-treat population; SD=standard deviation
Responder Analysis (mITT)

- Significantly higher proportion of patients in omalizumab 150 mg and 300 mg groups had symptoms which were well controlled (UAS7≤6) vs. placebo

- A large proportion of patients treated with omalizumab 300 mg were completely symptom free (UAS7=0) by Week 12

UAS7≥6 (secondary endpoint)

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of patients with UAS7≤6 at Week 12</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>OMA 75 mg</td>
<td>26.8</td>
<td>0.34</td>
</tr>
<tr>
<td>OMA 150 mg</td>
<td>42.7</td>
<td>0.001</td>
</tr>
<tr>
<td>OMA 300 mg</td>
<td>65.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

UAS7=0 (post-hoc analysis)

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of patients with UAS7=0 at Week 12</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>OMA 75 mg</td>
<td>15.9</td>
<td>0.03</td>
</tr>
<tr>
<td>OMA 150 mg</td>
<td>22.0</td>
<td>0.002</td>
</tr>
<tr>
<td>OMA 300 mg</td>
<td>44.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

mITT=modified intention-to-treat population; OMA=omalizumab; PBO=placebo; UAS7=weekly urticaria activity score
Summary of Efficacy and Safety of Omalizumab in Asteria II Study for CIU/CSU

• Omalizumab improved primary and secondary endpoints in a consistent dose-dependent fashion:
  ▪ 300 mg improved all endpoints
  ▪ 150 mg improved all endpoints except angioedema
  ▪ 75 mg did not meet the primary endpoint

• Rapid onset of treatment effect
  ▪ Within 1 week for 300 mg dose

• Symptom scores increased towards placebo after Week 12

• No new safety issues or concerns were identified compared to the known safety profile of omalizumab in the allergic asthma patient population
Down regulation of the high-affinity IgE receptor associated with successful treatment of chronic idiopathic urticaria with omalizumab

Michael C Saavedra*, Sanjiv Sur
Figure 1 Mean expression of FcεRI prior to treatment with omalizumab. Peripheral blood was collected from the patient and a normal control subject prior to the patient’s first treatment with omalizumab. Total FcεRI expression was examined in whole blood by flow cytometry using dual staining with basophil cell surface markers anti-CD123 (IL-3r) and anti-FcεRI.
Figure 2 Change in FcεRI expression during treatment with omalizumab. Whole blood was collected from the patient prior to the first treatment with omalizumab (day 0) and prior to each subsequent treatment day. Total FcεRI expression was examined in whole blood by flow cytometry using dual staining with basophil cell surface markers anti-CD123 (IL-3r) and anti-FcεRI.
Other Types of Urticaria

- At least 2 cases in solar urticaria (Waibel et al. JACI 2010)
- Cold-induced urticaria (Boyce JACI 2006)
- Cholinergic urticaria (Otto et al. Allergy Asthma Proc 2009)
Anti-Immunoglobulin E Treatment of Patients with Recalcitrant Physical Urticaria

Martin Metz  Sabine Altrichter  Elena Ardelean  Birgit Kessler  Karoline Krause
Markus Magerl  Frank Siebenhaar  Karsten Weller  Torsten Zuberbier  Marcus Maurer

Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany
“So many people ask me about my autoimmune disease - chronic urticaria - it’s like a giant rash all over your body. And this is how it works…”
RISERVE
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 Rosén, MD, PhD Charleston, SC, Tampa, Fla, South San Francisco and Mission Viejo, Calif, Horsham and Welwyn Garden City, United Kingdom, Mainz, Freiburg, and Berlin, Germany, Melbourne, Australia, and Lodz, Poland
Study Design

Screening Period
2 Weeks

Treatment Period
24 Weeks

Follow-Up Period
16 Weeks

Day -14 Day 1 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24 Week 40

Treatment administered every 4 weeks for total of 6 doses: placebo or omalizumab 300 mg

Week 24: primary endpoint assessment

Patients continued stable doses of H1-antihistamines, H2 antihistamines and/or LTRA throughout treatment period and were permitted rescue DPH 25 mg up to 3 doses/day

DPH=diphenhydramine
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age years</th>
<th>Duration of disease years</th>
<th>Previous medication</th>
<th>Total IgE kU/l</th>
<th>Omalizumab dose</th>
<th>Type of physical urticaria</th>
<th>Positive after provocation with</th>
<th>Threshold after treatment</th>
<th>Complete symptom control</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>M/29</td>
<td>27</td>
<td>1a, b; 2a, b; 3b; 4b; 7a</td>
<td>322</td>
<td>300 mg/month</td>
<td>solar</td>
<td>2.4 J/cm² UVA</td>
<td>&gt;6 J/cm² (not detectable)</td>
<td>yes</td>
</tr>
<tr>
<td>B</td>
<td>W/63</td>
<td>5</td>
<td>1a; 2a; 3a; b; 4a; 5a; b; 6a; 10c; 11c; d; 12</td>
<td>111</td>
<td>300 mg every 2 weeks</td>
<td>heat contact</td>
<td>38°C</td>
<td>40°C</td>
<td>no</td>
</tr>
<tr>
<td>C</td>
<td>M/19</td>
<td>4</td>
<td>1a; 2a; 3a; b; 7a, b</td>
<td>64</td>
<td>150 mg/month</td>
<td>cold contact</td>
<td>&lt;4°C (not detectable)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>W/55</td>
<td>15</td>
<td>1a; 2a; 3a; b; 4a; b; 5a; b; 6a; 7a; b; 12</td>
<td>22</td>
<td>150 mg every 2 weeks</td>
<td>solar</td>
<td>&gt;6 J/cm² (not detectable)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>W/38</td>
<td>5</td>
<td>1a, b; 2a, b; 3a, b; 5a, b; 8a; 9c; 10d; 11</td>
<td>90.5</td>
<td>150 mg/month</td>
<td>delayed pressure</td>
<td>14.8 kPa (after 4 h)</td>
<td>not detectable</td>
<td>yes</td>
</tr>
<tr>
<td>F</td>
<td>W/49</td>
<td>4</td>
<td>1a; 2a; 3a; b; 4a; b; 5; 7a, b; 8a; 10c; 11d</td>
<td>245</td>
<td>300 mg/month</td>
<td>urticaria factitia</td>
<td>dermographometer (graded, 2/4 positive)</td>
<td>not detectable</td>
<td>yes</td>
</tr>
<tr>
<td>G</td>
<td>W/46</td>
<td>2</td>
<td>1a; 2a; 3a; b; 4a; b; 5a; b; 7a, b; 8a; 10c; 11d</td>
<td>20</td>
<td>150 mg/month increased to 300 mg/month</td>
<td>urticaria factitia</td>
<td>1/4 positive</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

1 = Loratadine; 2 = cetirizine; 3 = desloratadine; 4 = ebastine; 5 = rupatadine; 6 = levocetirizine; 7 = fexofenadine; 8 = hydroxyzine; 9 = clemastine; 10 = ranitidine; 11 = montelukast; 12 = antibiotics; a = standard dose; b = high dose (2–6-fold increased); c = in combination with H₁ antihistamines; d = in combination with H₁ and H₂ blocker.
Omalizumab Responder Analysis

A

Patients with UAS7≤6 at Week 12 (%)

- Placebo
- Omalizumab 300 mg

B

Patients with UAS7=0 at Week 12 (%)

- Placebo
- Omalizumab 300 mg
Fig. 1. Provocation tests with assessment of thresholds. 

a, b Graded testing in a patient with urticaria factitia (symptomatic dermographism) before and after treatment with omalizumab. Before treatment (a; the patient used non-sedating antihistamines twice daily), wheal development can be observed in lines 2, 3 and 4; after treatment (b), wheal development can be observed only in line 4 and erythema in lines 2 and 3. 

c, d Threshold UV testing (UVA and UVB) in a patient with solar urticaria before (c) and after (d) treatment with omalizumab. 

e, f Assessment of critical temperature thresholds in cold urticaria patients. 

e Example of a positive cold stimulation test using TempTest® with a critical temperature threshold of 22°C. 

f Cold stimulation test in our patient with cold urticaria after omalizumab treatment. Before treatment, the critical temperature threshold was 16°C, as measured by TempTest (no image available).
Original article

A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H₁-antihistamine-refractory chronic idiopathic urticaria

Sarbjit Saini, MD, Karin E. Rosen, MD, PhD, Hsin-Ju Hsieh, PhD, Dennis A. Wong, MD, Edward Conner, MD, Allen Kaplan, MD, Sheldon Spector, MD, and Marcus Maurer, MD

Baltimore, Md, South San Francisco and Los Angeles, Calif, Charleston, SC, and Berlin, Germany
Methods

• Phase IIa prospective, DB, placebo controlled dose ranging study in patients with chronic urticaria not responsive to antihistamines using single dose of omalizumab

• 75mg, 300 mg, and 600 mg omalizumab

• Change in UAS from baseline to 4 weeks
FIG 3. Mean ± SD for changes from baseline to week 4 in UAS7. *P* values are based on comparison with the placebo group by using the Van Elteren test. *OMA*, Omalizumab.
FIG 5. Mean ± SD for changes from baseline to week 4 in weekly itch and weekly hive scores. $P$ values are based on comparison with the placebo group by using the Van Elteren test.