

# A Study of 105 Patients Treated with Omalizumab for Chronic Idiopathic Urticaria

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**Abstract:** Omalizumab (Xolair®) was approved for the treatment of chronic idiopathic urticaria in 2017. Furthermore, consistent with international guidelines published in 2018, the Urticaria Clinical Practice Guidelines by the Japanese Dermatological Association provide detailed instructions for the use of omalizumab. However, there are no reports summarizing the efficacy of omalizumab in chronic idiopathic urticaria in Japan. The subjects of our study were 105 patients treated with omalizumab 300 mg/month for chronic idiopathic urticaria at Tokyo Medical University Hospital from June 2017 to March 2021, inclusive of 23 male and 82 female patients, with a mean age of  $45.4 \pm 16.0$  and disease duration of  $46.9 \pm 99.4$  months. Three months after treatment, omalizumab was discontinued in 63 patients with a Urticaria Control Test score of 16. The mean number of dose completions was  $6.4 \pm 4.1$ . There were nine cases of relapse in which seven of the nine cases discontinued omalizumab within six doses. Most of the relapsed cases improved with re-administration of omalizumab, but it was again discontinued in five cases. Omalizumab has lesser side effects than steroids and cyclosporine, and the criteria for its use were revised in 2018, requiring an allergist or dermatologist to be available to treat adverse events such as asthma and anaphylaxis at the facility or in collaboration with neighboring medical institutions. Omalizumab can also be used in dermatology clinics. The drug is an effective treatment for severe chronic idiopathic urticaria and is anticipated to be used by more dermatologists.

**Keywords:** Chronic spontaneous urticaria; Omalizumab; Clinical statistics

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## 1. Introduction

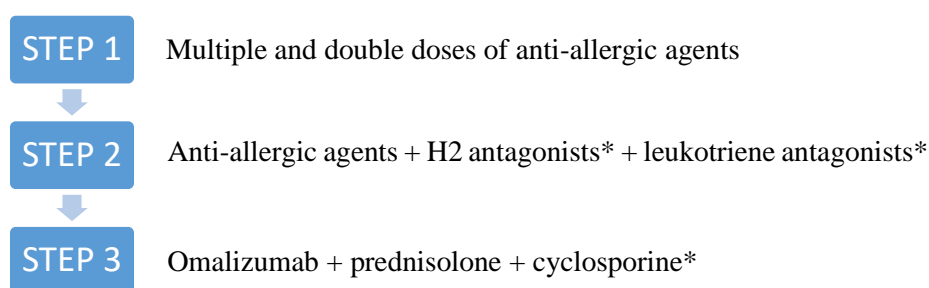
Chronic idiopathic urticaria is the most common form of urticaria seen at medical institutions and is characterized by a skin rash lasting more than six weeks with no known causative antigen<sup>[1]</sup>. The 2018 Urticaria Clinical Practice Guidelines published by the Japanese Dermatological Association clearly describe the treatment strategy and are consistent with international guidelines<sup>[2]</sup>, making them useful in daily practice. Omalizumab was launched in 2009 as the first antibody product for treating allergic diseases. In 2017, omalizumab was also approved for the treatment of chronic idiopathic urticaria, and it was found effective in treatment-resistant chronic idiopathic urticaria. In 2018, the Japanese Academy of Dermatology and the Japanese Society of Allergology revised the criteria for the use of omalizumab, making it possible to administer the drug at dermatology clinics, with close considerations to its safety. The efficacy and effectiveness of omalizumab have been reported in many cases<sup>[3,4]</sup>. In Japan, omalizumab has been used without major side effects, but there have been no reports specifically analyzing its efficacy.

In this study, we report on 105 patients with chronic idiopathic urticaria treated with omalizumab in our department, and the frequency of omalizumab administration and recurrent cases were investigated to

determine its efficacy.

## 2. Methods

In this study, we included 105 patients with chronic idiopathic urticaria treated with omalizumab 300 mg/month in combination with H1 antagonists, H2 antagonists, and antileukotrienes (in cases where the three-drug combination was ineffective) at Tokyo Medical University Hospital from June 2017 to March 2021. The indicators observed were gender, mean age, duration of disease, treatment history, response to omalizumab, last total number of doses, and relapse. Patients receiving only H1 antagonist at the first visit were given a double dose of H1 antagonist, in combination with H2 antagonist and antileukotriene, and omalizumab was prescribed to those who did not respond within 2 weeks. Patients on H1 antagonist, H2 antagonist, and antileukotriene at the time of initial diagnosis were often already on multiple H1 antagonists. Patients who did not require any change in medication after history-taking were treated with omalizumab on the same day. This study was approved by the Ethics Committee of Tokyo Medical University (approval number T2020-0427), and the department adhered to the 2018 urticaria guidelines by the Japanese Dermatological Association (**Figure 1**).



**Figure 1.** Treatment for idiopathic chronic idiopathic urticaria <sup>[1]</sup> (\*not covered by insurance)

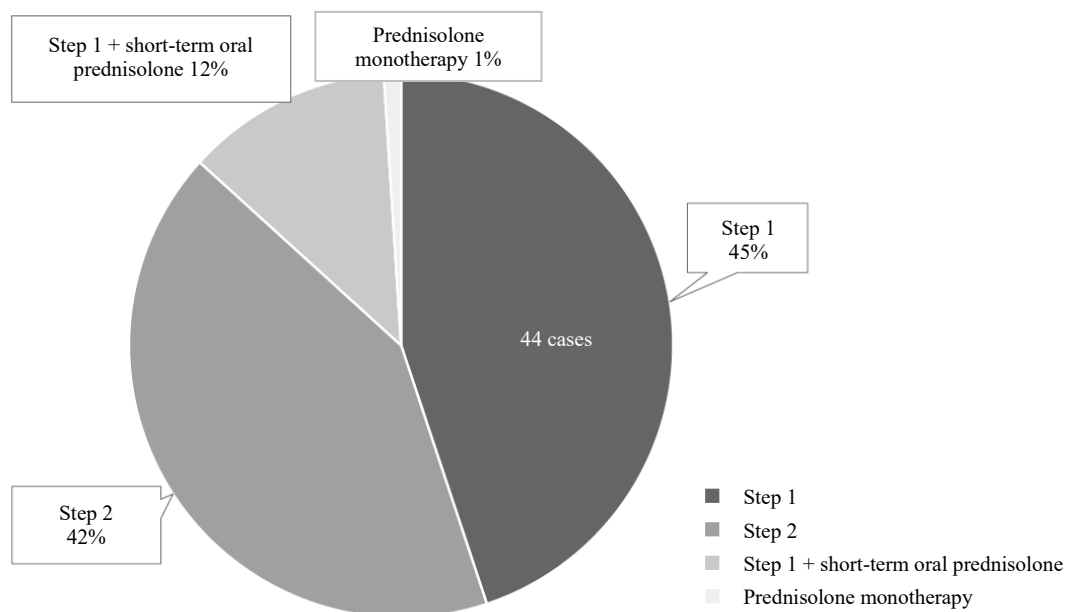
## 3. Results

### 3.1. Patient background

Patients treated with omalizumab were 3.6 times more likely to be female (82 patients) than male (23 patients). The mean age was  $45.4 \pm 16.0$ , and the duration of disease was  $46.9 \pm 99.4$  months.

### 3.2. Treatment history

In terms of the treatment history of the patients treated with omalizumab, 98 (93%) patients had been treated before coming to our hospital, while the remaining 7 had not been treated previously. According to the urticaria guideline for the treatment of chronic idiopathic urticaria, the combination and double-dose treatment with multiple anti-allergic agents (H1 antagonists) was defined as STEP 1; the triple-drug combination treatment with anti-allergic agents (H1 antagonists), H2 antagonists (not covered by insurance), and leukotriene antagonists (not covered by insurance) was defined as STEP 2; and the combination therapy with omalizumab, prednisolone (not covered by insurance), and cyclosporine (not covered by insurance) was defined as STEP 3. After reviewing the details of treatment by the previous physician, 44 cases (45%) were referred to our department due to poor control after STEP 1, 41 cases (42%) were referred due to poor control after STEP 2, 12 cases (12%) were poorly controlled under STEP 3 treated with anti-allergic agents and prednisolone  $< 0.2$  mg/kg/day for 1 week; 1 case (1%) showed inadequate response to prednisolone monotherapy (**Figure 2**).



**Figure 2.** Previous treatment

The treatment details for STEP 1, 2, and 3 were based on the 2018 urticaria guidelines. Step 1 + prednisolone treatment was discontinued within 1 week in all patients with prednisolone < 0.2 mg/kg/day.

### 3.3. Efficacy of treatment with omalizumab

We used the Urticaria Control Test (UCT) as an indicator after the initiation of omalizumab due to poor control after STEP 2. The UCT is a simple and reliable questionnaire that assesses patients' disease control over a 4-week period (**Table 1**). All patients scored less than 8.

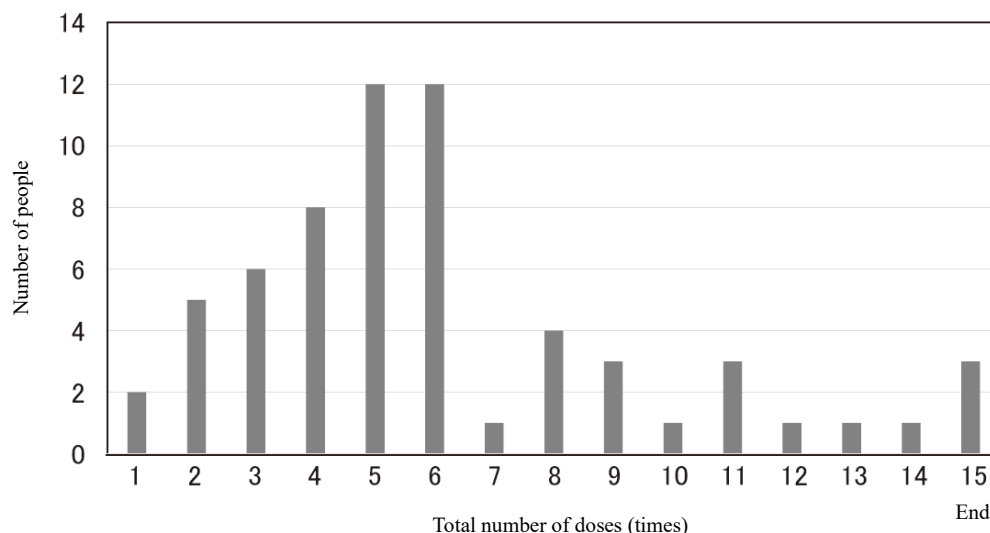
**Table 1.** Urticaria Control Test (UCT)

|   |              |               |              |                |
|---|--------------|---------------|--------------|----------------|
| Please choose the answer that best fits your situation during the last four weeks from the following questions: |              |               |              |                |
| Q1. How much have you suffered from the physical symptoms of urticaria (itching, wheals, and/or swelling)?      |              |               |              |                |
| (0) Very much   | (1) Much     | (2) Somewhat  | (3) A little | (4) Not at all |
| Q2. How much has your quality of life been affected by urticaria?   |              |               |              |                |
| (0) Very much   | (1) Much     | (2) Somewhat  | (3) A little | (4) Not at all |
| Q3. How often was the treatment for your urticaria insufficient to control your urticaria symptoms?             |              |               |              |                |
| (0) Very often  | (1) Often    | (2) Sometimes | (3) Rarely   | (4) Not at all |
| Q4. How well was your urticaria kept under control?   |              |               |              |                |
| (0) Not at all  | (1) A little | (2) Somewhat  | (3) Well     | (4) Very well  |

Score:  $\geq 12$  points, good control; 8–11 points, some degree of control; < 8 points: poor control.

During the observation period from June 2017 to March 2021, 63 patients completed omalizumab treatment, 33 continued treatment, and 9 discontinued treatment. "Improvement" was defined as no wheals for 2 weeks after omalizumab treatment. There were 63 (60%) cases of improvement after the first dose, 16 (15%) cases of improvement after the second dose, 12 (11%) cases of improvement after the third dose, and 14 (13%, including cases of continuous treatment) cases without any change.

Patients with a UCT of 16, *i.e.*, no wheals at all during the first 3 months of treatment, discontinued omalizumab treatment and were transferred to STEP 2. The mean number of doses completed was  $6.4 \pm 4.1$ . **Figure 3** shows the total number of doses administered in the 63 cases of improvement: some cases improved after 10 or more doses, but the highest incidence (12 people each) was after 5 or 6 doses.



**Figure 3.** Total number of doses of omalizumab observed in 63 patients who completed treatment within the observation period.

### 3.4. Relapsed cases treated with omalizumab

Out of the 63 patients who completed omalizumab treatment, 9 relapsed (**Table 2**). The mean age was  $48.2 \pm 16$ , and the mean disease duration was  $42.2 \pm 47.2$  months.

**Table 2.** Cases of relapse with omalizumab treatment

| Cases | Gender | Age | Duration of disease | Total serum IgE | Underlying disease        | Number of doses | Time to relapse (months) | Total number of doses (times) |
|-------|--------|-----|---------------------|-----------------|---------------------------|-----------------|--------------------------|-------------------------------|
| 1     | F      | 39  | 2                   | 55.1            | Depression                | 3 times         | 2 months                 | End of 10th                   |
| 2     | M      | 80  | 60                  | 85.3            | None                      | 3 times         | 2 months                 | 10th ongoing                  |
| 3     | M      | 29  | 2                   | 56.6            | Asthma, allergic rhinitis | 3 times         | 1 months                 | 9th ongoing                   |
| 4     | F      | 49  | 60                  | 36              | Diabetes mellitus         | 4 times         | 16 months                | 11th ongoing                  |
| 5     | M      | 73  | 2                   | 384             | None                      | 4 times         | 2 months                 | 6th ongoing                   |
| 6     | F      | 38  | 120                 | 33.2            | Allergic anisakiasis      | 6 times         | 2 months                 | End of 9th                    |
| 7     | F      | 45  | 120                 | 286             | Hay fever                 | 6times          | 4 months                 | End of 11th                   |
| 8     | M      | 38  | 2                   | 109             | None                      | 7 times         | 1 months                 | End of 14th                   |
| 9     | F      | 43  | 12                  | Unexamined      | None                      | 8 times         | 4 months                 | End of 11th                   |

The underlying medical conditions varied from depression, asthma, diabetes mellitus, and hay fever to no autoimmune diseases. The total serum immunoglobulin E (IgE) before omalizumab treatment ranged from 36 IU/mL to 384 IU/mL, with no consistent trend. Out of the nine cases, omalizumab was discontinued in seven patients after six or fewer doses. The mean number of doses in all nine patients was  $4.89 \pm 1.79$ ,

and the time until relapse was  $3.78 \pm 4.44$  months (1–16 months). Omalizumab was again discontinued in five of the nine patients, with a mean of 11 doses.

#### 4. Discussion

Chronic idiopathic urticaria accounts for the majority of urticaria cases. According to statistics from the outpatient dermatology department at Hiroshima University <sup>[5]</sup>, chronic idiopathic urticaria accounts for more than 50% of all urticaria cases. However, the exact etiology of chronic idiopathic urticaria is unknown. In view of the current hypothesis, it can be classified into Type I autoimmunity and Type II autoimmunity, with the former being an antigen/IgE reaction resulting in a runaway autoimmune response and an increase in mast cell degranulation, while the latter resulting in the formation of autoantibodies against IgE (IgG anti-IgE) and degranulation due to IgE crosslinking. The development of autoantibodies against the IgE receptor FcεRI (IgG anti-FcεRI), resulting in degranulation due to IgE crosslinking, is also considered to be a pathogenic factor <sup>[6]</sup>. In Japanese patients, autoantibodies against IgE (IgG anti-IgE) have been observed and reported to cause chronic idiopathic urticaria <sup>[7]</sup>.

Recently, it has been reported that anti-interleukin (IL)-24 IgE antibody levels correlate with chronic idiopathic urticaria activity <sup>[8]</sup>. IL-24 has no specific receptor and binds to heterodimers of IL-20 and IL-22 receptors <sup>[9]</sup>. In a study, patients with chronic idiopathic urticaria demonstrated higher serum anti-IL-24 IgE levels, which showed a positive correlation with the Urticaria Activity Score for clinical symptoms <sup>[8]</sup>. Furthermore, there have been reports of blood coagulation involvement in the pathogenesis of chronic idiopathic urticaria <sup>[10]</sup>. The pathophysiology of the disease is still being elucidated.

The response to chronic idiopathic urticaria treatment varies between individuals. In 2018, Folci *et al.* proposed several severity indicators of chronic idiopathic urticaria. In clinical terms, severe and refractory cases include (i) elderly patients, (ii) women, (iii) patients with disease duration of more than one year, (iv) patients with Quincke's oedema, and (v) patients with aspirin intolerance; in molecular terms, D-dimer (not covered by insurance) and C-reactive protein (CRP; not covered by insurance) are blood samples that can be collected in clinics <sup>[11]</sup>. Knowledge of the severity indicators of clinical symptoms enables clinicians to provide the approximate duration of treatment to the patients.

In the present study, according to the severity indicators reported by Folci *et al.*, women were 3.5 times more likely to be in the severe group, with a mean disease duration of 3.8 years. As shown in **Figure 2**, 45% of the patients were referred due to poor control after STEP 1 (double dose of anti-allergic agents or multiple drugs), and 42% were referred for due to poor control after STEP 2 (triple combination of anti-allergic agents, leukotriene antagonists, and H2 antagonists). In 2020, we reported an efficacy analysis of 60 patients treated with omalizumab in our department <sup>[12]</sup>. In that study, 27% of patients were referred for STEP 2. In the following two years, omalizumab was newly introduced in 40 patients, but recently, patients were treated up to STEP 2 in clinics, and only refractory cases were referred to our hospital. We considered that an increasing number of dermatologists were treating patients in accordance with the 2018 urticaria guidelines <sup>[1]</sup>. In addition, this hospital actively holds meetings for regional medical cooperation. Dermatologists and physicians in the neighborhood have many patients with chronic idiopathic urticaria, who have been reportedly struggling with the treatment of the disease. As a result of several talks on the introduction and effectiveness of omalizumab, confirmation of initial treatment according to the guidelines, and the timing of referral to a university hospital, we have received referrals from general practitioners in the neighborhood, mostly when treatment in STEP 1 or 2 is ineffective, in collaboration with medical diagnostics. No cases of long-term low-dose steroids were observed. The guidelines for starting omalizumab are as described above in section 2. Recently, there is a tendency for general practitioners to refer only poorly controlled cases to our hospital after STEP 2 and the referring practitioner to continue patient care only when omalizumab treatment is completed and the patient is on oral therapy.

In our study, 60% of patients had a marked improvement in wheals after the first dose. However, many cases relapsed after three weeks, which may be related to the pharmacokinetics of omalizumab, which has a half-life of 21 days. We, therefore, decided to terminate treatment only in patients who scored 16 on UCT for 3 months after starting omalizumab treatment, reduce the treatment step from 3 to 2, and use oral treatment only. This resulted in a final total number of doses of  $6.4 \pm 4.1$ . There have been no reports in Japan on how long before omalizumab can be discontinued. Based on the results of this study, although there may be individual differences depending on the severity of the disease, omalizumab treatment should be stopped if there are no wheals for three months, with an initial target of six to seven doses. This makes patients more positive about treatment and makes it easier to adjust the schedule.

In a study of relapsed cases, seven out of nine patients discontinued after six or fewer doses. The advantage of treatment with omalizumab is that it is effective even after relapse<sup>[13]</sup>. The etiology of chronic idiopathic urticaria is not IgE-dependent, and total serum IgE levels vary considerably between patients. The efficacy of omalizumab in patients with total serum IgE below 15.2 IU/mL was found to be very low<sup>[14]</sup>, half that of patients with total serum IgE between 50–4,000 IU/mL. In another report, the response to treatment with omalizumab was found to be better in patients with a higher-percentage increase in total serum IgE after treatment compared to before treatment<sup>[15]</sup>. As stated in the report, patients with high IgE levels and a high percentage of elevated IgE do not respond better to treatment, although it is advisable to administer omalizumab to patients with low total serum IgE levels after a detailed explanation of the efficacy, *etc.*, while measuring total IgE levels<sup>[15]</sup>. It is important to note that although total IgE measurements and elevation rates are useful in predicting treatment response, they are not 100% reliable. In our study of recurrent cases, there was no underlying disease or consistent trend in age, sex, duration of disease, underlying disease, or total serum IgE levels. According to the severity indicators reported by Folci *et al.*, cases 3 and 5 (as listed in **Table 2**) responded to treatment but did not complete omalizumab despite being male, having short disease duration, a total IgE level of more than 15.2 IU/mL, and being in the well-treated group. A similar series of cases should be accumulated in the future.

The criteria for the availability of omalizumab were revised in 2018, stating that it must be used by an allergist or dermatologist at a facility or in collaboration with a neighboring medical institution under a system that can respond to adverse events such as asthma, anaphylaxis, *etc.*, and that it can also be used in dermatology clinics. Since the drug is an effective treatment for severe chronic idiopathic urticaria, it is recommended that more dermatologists use it.

## Disclosure statement

The authors declare no conflict of interest.

## References

- [1] Japanese Dermatological Association Urticaria Clinical Practice Guideline Revision Committee, 2018, Urticaria Clinical Practice Guidelines 2018. *Journal of the Japan Skin Association*, 128(12): 2503–2624.
- [2] Zuberbier T, Aberer W, Asero R, et al., 2018, The EAACI/GA<sup>2</sup>LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. *Allergy*, 73(7): 1393–1414.
- [3] Kaplan A, Ledford D, Ashby M, et al., 2013, Omalizumab in Patients with Symptomatic Chronic Idiopathic/Spontaneous Urticaria Despite Standard Combination Therapy. *J Allergy Clin Immunol*, 132(1): 101–109.
- [4] Nettis E, Cegolon L, Di Leo E, et al., 2018, Omalizumab in Chronic Spontaneous Urticaria: Efficacy,

- Safety, Predictors of Treatment Outcome, and Time to Response. *Ann Allergy Asthma Immunol*, 121(4): 474–478.
- [5] Tanaka T, Kameyoshi Y, Hide M, 2006, Analysis of the Prevalence of Subtypes of Urticaria and Angioedema. *Allergy*, 55(2): 134–139.
- [6] Kolkhir P, Church MK, Weller K, et al., 2017, Autoimmune Chronic Spontaneous Urticaria: What We Know and What We Don't Know. *J Allergy Clin Immunol*, 139(6): 1772–1781.
- [7] Izaki S, Toyoshima S, Endo T, et al., 2019, Differentiation Between Control Subjects and Patients with Chronic Spontaneous Urticaria Based on the Ability of Anti-IgE Autoantibodies (AAbs) to Induce FcεRI Crosslinking, as Compared to Anti-FcεRIα AAbs. *Allergol Int*, 68(3): 342–351.
- [8] Schmetzer O, Lakin E, Topal FA, et al., 2018, IL-24 is a Common and Specific Autoantigen of IgE in Patients with Chronic Spontaneous Urticaria. *J Allergy Clin Immunol*, 142(3): 876–882.
- [9] Wang M, Liang P, 2005, Interleukin-24 and Its Receptors. *Immunology*, 114(2): 166–170.
- [10] Yanase Y, Morioke S, Iwamoto K, et al., 2018, Histamine and Toll-like Receptor Ligands Synergistically Induce Endothelial Cell Gap Formation by the Extrinsic Coagulating Pathway. *J Allergy Clin Immunol*, 141(3): 1115–1118.
- [11] Folci M, Heffler E, Canonica GW, et al., 2018, Cutting Edge: Biomarkers for Chronic Spontaneous Urticaria. *J Immunol Res*, 21: 5615109.
- [12] Ito T, Okubo Y, Harada K, 2020, A Study of Patients Treated with Omalizumab for Chronic Idiopathic Urticaria Experienced in Our Department. *Journal of the Japan Skin Association*, 130: 1217.
- [13] Maurer M, Kaplan A, Rosén K, et al., 2018, The XTEND-CIU Study: Long-Term Use of Omalizumab in Chronic Idiopathic Urticaria. *J Allergy Clin Immunol*, 141(3): 1138–1139.
- [14] Straesser MD, Oliver E, Palacios T, et al., 2018, Serum IgE as an Immunological Marker to Predict Response to Omalizumab Treatment in Symptomatic Chronic Urticaria. *J Allergy Clin Immunol Pract*, 6(4): 1386–1388.
- [15] Weller K, Ohanyan T, Hawro T, et al., 2018, Total IgE Levels Are Linked to the Response of Chronic Spontaneous Urticaria Patients to Omalizumab. *Allergy*, 73(12): 2406–2408.

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