Chen et al. World Allergy Organization Journal (2021) 14:100501
http://doi.org/10.1016/j.waojou.2020.100501

WORLD ALLERGY ORGANIZATION JOURNAL

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Omalizumab treatment and outcomes in Chinese patients with chronic spontaneous urticaria, chronic inducible urticaria, or both

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ABSTRACT

Background: Chronic urticaria (CU) is a common skin disorder, which can be further divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). Omalizumab is effective and safe for difficult-to-treat CSU based on clinical trials. However, there are limited data comparing the therapeutic effect of omalizumab for patients with CSU, CIndU, and CSU plus CIndU. Meanwhile, there is still no reliable predictor for treatment response or relapse. Our study was conducted to collect real-world clinical data on omalizumab treatment in patients with CSU, CIndU, and both.

Methods: This was an observational, retrospective chart review of patients with CU initiating omalizumab treatment between February 2018 and May 2020 (maximum 28 months follow-up).

Results: A total of 138 patients were included, 87 with CSU alone, 33 with different forms of CIndU, and 18 with both. A total of 87.0% (n = 120/138) of the CU patients responded to omalizumab therapy, among which 65.2% (n = 90/138) of the patients showed complete response and 21.7% (n = 30/138) of the patients showed partial response. The therapeutic effect and speed of onset of effect for omalizumab were comparable among patients with CSU, CIndU, or both. Autologous serum skin test (ASST)-positive patients were more likely to show a slow response to omalizumab therapy ($P = 0.043$). Non-responders had lower baseline total IgE levels (35.0 vs 121.5 kU/L, $P < 0.001$). The proportion of patients with low total IgE levels in non-responders was significantly higher than that of responders (61.1% vs. 14.5%, $P < 0.001$). Also, more non-responder patients had elevated thyroid autoantibodies than responders (50.0% vs. 23.0%, $P = 0.041$). The median ratio of serum IgG-anti-TPO to serum total IgE in non-responders was significantly higher compared with responders (1.22 vs. 0.09, $P < 0.001$). Non-responders also had shorter treatment periods (4.5 vs 6.0 months, $P = 0.035$) compared with responders. Two of 3 patients (67.4%, n = 29/43) experienced relapse after ceasing omalizumab therapy. These patients had longer disease durations (52.0 vs. 15.0 months, $P = 0.007$) and higher baseline total IgE levels (179.9 vs. 72.5 kU/L, $P = 0.020$) than patients who did not relapse. We reinitiated omalizumab

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Full list of author information is available at the end of the article https://doi.org/10.1016/j.waojou.2020.100501

http://doi.org/10.1016/j.waojou.2020.100501
Received 13 September 2020; Received in revised from 18 November 2020; Accepted 3 December 2020
Online publication date xxx
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treatment for 10 relapsed patients, all of them reported a rapid response after the first injection within the first 4 weeks of retreatment.

Conclusion: Omalizumab is highly effective in patients with difficult-to-treat CSU, CIndU, or both. Responders tend to have unique immunological features and longer treatment periods. Patients with higher baseline total IgE levels and longer disease durations are more likely to experience rapid relapse after discontinuation of omalizumab.

Keywords: Chronic urticaria, Omalizumab, Dermatology life quality index, Urticaria control test

INTRODUCTION

Chronic urticaria (CU) is characterized by the recurrence of itchy wheals, angioedema, or both for more than 6 weeks. The prevalence of CU in Asia is 1.4%, higher than that in Europe (0.5%) and North America (0.1%).[1] It is divided into 2 types, chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU)–the latter including, for example, cold urticaria, cholinergic urticaria, and symptomatic dermographism.[2] CU markedly impairs quality of life (QoL) with significant impact on sleep, work performance, and social interactions.

The EAACI/GA^{2}LEN/EDF/WAO urticaria guideline recommends approved doses of second-generation H_1-antihistamines as the first-line treatment for CU, and up to 4 times the approved dose as the second-line treatment.[2] However, a significant proportion of patients continue to experience symptoms even with high-dose antihistamine treatment and require more effective therapies.[3,4] According to the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline, omalizumab is recommended as the only third-line therapy option for patients with antihistamine-resistant CU.[2]

Omalizumab (Xolair®) is a recombinant humanized monoclonal anti-IgE antibody that binds circulating free IgE and downregulates the high-affinity receptor for IgE (FcϵRI).[5,6] The clinical efficacy and safety of omalizumab in CSU has been shown in several clinical trials and real-life studies.[7-12]

Our study was conducted to evaluate the efficacy and time of response to omalizumab in Chinese patients with CSU, CIndU, or both, who had an inadequate response to H_1-antihistamine treatment. The recently validated Chinese version of urticaria control test (UCT) was used to assess disease control status in this retrospective clinical study.[13] Additionally, the present study provides information on drugs used in combination with omalizumab, relapse, retreatment and potential predictors of response and recurrence of symptoms after omalizumab discontinuation.

MATERIALS AND METHODS

Study design

This was a retrospective, observational, investigator-initiated study examining real-world treatment scenarios of antihistamine-resistant CU in China. The data for this study were retrieved retrospectively from patients' medical records. The study was approved by the China Ethics Committee of Registering Clinical Trials (IRB: ChiECRCT20190131). The review board waived the need for informed consent. The study was designed, implemented, and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology and the STROBE guidelines.

Patients

We included 138 adult patients with CSU, CIndU, or both who had received at least 1 injection of omalizumab and had at least 1 follow-up visit between February 2018 and May 2020. Preliminary results on the outcome of omalizumab treatment in some of the patients analysed here were reported previously.[14] CU was diagnosed based on the patients' history and clinical picture according to the EAACI/GA^{2}LEN/EDF/WAO

urticaria guideline; other diseases and syndromes presenting with wheals, angioedema or both (eg, urticarial vasculitis, Schnitzler's syndrome, cryopyrin-associated periodic syndromes, bradykinin-mediated angioedema) were ruled out. In patients with CIndU, specific provocation tests were performed to verify the diagnosis. Provocation tests and threshold testing were performed using a FricTest® (Moxie, Berlin, Germany) for symptomatic dermographism, a TempTest® (Courage & Khazaka, Berlin, Germany) for cold and heat urticaria, and physical exercise provocation test for cholinergic urticaria. To be started on omalizumab therapy, patients had to be unresponsive to second generation H_1-antihistamines (SGAHs). Patients were excluded if they were participating in any clinical trials for CU during the observation period or if they were treated with omalizumab for any other indication (eg, allergic asthma, allergic rhinitis).

Assessment of treatment efficacy and relapse

The urticaria control test (UCT) was applied to assess disease control status for all CU patients.[13,15] The UCT has a 4-week recall period and consists of 4 questions, each with 5 answer options (scored 0–4 points), where low points indicate high disease activity and poor disease control. The minimum and maximum UCT score is 0 and 16, respectively. A "complete response" was defined by UCT = 16 during the period of treatment with omalizumab, with/without H_1-antihistamine therapy. A "partial response" was defined as UCT $\geq$12 during omalizumab treatment period, with/without H_1-antihistamine therapy. "Nonresponse" was defined as UCT $<$12 during omalizumab treatment. Patients who showed complete response or partial response were considered as "responders". Patients with CSU also completed the urticaria activity score (UAS) once daily, and the 7-day UAS (UAS7) was calculated.

Patients' QoL was assessed by the dermatology life quality index (DLQI) during the study period.[16] A DLQI of 21–30 indicates extremely large impairment of patients' QoL, 11–20 indicates very large impairment, 6–10 implies moderate impairment, 2–5 implies small effect on patients' QoL, and 0–1 marks no effect at all on patient's QoL.[16]

Relapse was defined as the reappearance of CU symptoms (UCT $<$ 12) in complete responders after discontinuation of omalizumab treatment.

Laboratory data

Serum total IgE was measured by a chemiluminescent immunoassay (ImmunoCAP; ThermoFisher Scientific, Sweden), and levels of 100 kU/L or greater were defined as increased. Autologous serum skin test (ASST) was performed through the intracutaneous injection of autologous serum as described previously.[17] Thyroid autoantibodies including serum thyroid peroxidase antibody and thyroglobulin antibody were determined using an electrochemiluminescence immunoassay (Roche Elecsys-2010; Roche Diagnostics, U.S.) and the normal reference ranges were 0–34 IU/ml, and 0–115 IU/ml, respectively.

Data collection

Data were collected from clinical records of the patients. Demographics (age, sex), baseline urticaria profiles (disease duration, type of chronic urticaria, concomitant angioedema, total IgE level, levels of thyroid autoantibodies, ASST result, UCT, DLQI, and UAS scores) and omalizumab treatment patterns (treatment durations, drugs used in combination with omalizumab and adverse events) were retrieved.

Statistical analysis

Descriptive statistics included the mean $\pm$ standard deviation (SD) or median (interquartile range, IQR) as appropriate for continuous variables, as well as frequency (percentage) for categorical variables. Descriptive statistics were performed for demographic and different clinical variables including disease durations, concomitant angioedema, omalizumab treatment periods, types of urticaria, results of laboratory data, medications, relapse, and retreatment. For the analysis of clinical outcomes (UCT or DLQI), a Wilcoxon test was applied. Chi-square tests were used for group comparisons of categorical variables. The independent samples *t*-test or Mann–Whitney nonparametric test was used for comparisons of continuous variables between groups, as appropriate. Kaplan-Meier estimator and log-rank statistics were performed to analyse response time. Receiver-operator characteristic (ROC) curves

Characteristics	Overall (n = 138)	CSU (n = 87)	CIndU (n = 33)	CSU+CIndU (n = 18)
Age (years)	39.6 ± 13.4	44.3 ± 13.7	29.9 ± 7.6	34.8 ± 8.9
Female, n (%)	92 (66.7)	62 (71.3)	19 (57.6)	11 (61.1)
Disease duration (mo)	24 (12–56)	24 (12–66)	15 (12–36)	26 (18–51)
Angioedema, n (%) [a]	49 (35.5)	35 (40.2)	6 (18.2)	8 (44.4)
Omalizumab treatment periods (mo)	6.0 (4.0–11.0)	7.0 (4.0–12.0)	5.0 (2.5–8.0)	5.0 (3.5–7.0)
Baseline UCT	3.0 (0.0–4.0)	2.0 (0.0–4.0)	3.0 (1.5–5.0)	3.5 (1.0–4.3)
Baseline DLQI	18.0 (14.0–21.0)	18.0 (13.0–21.0)	19.0 (16.0–21.0)	18.5 (16.3–21.3)
Total IgE (kU/L) [b]	94.4 (48.9–309.0)	95.1 (42.0–320.0)	98.0 (68.5–313.0)	90.1 (47.1–259.8)
Elevated total IgE, n (%) [c]	61 (47.7)	40 (48.2)	13 (48.1)	8 (44.4)
ASST positive, n (%) [d]	47 (53.4)	30 (60.0)	9 (37.5)	8 (57.1)
Elevated thyroid autoantibodies, n (%) [e]	29 (27.6)	20 (26.7)	2 (15.4)	7 (41.2)

Table 1. Demographic data of patients with CSU, CIndU or both *Abbreviations: ASST: autologous serum skin test; CIndU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; DLQI, dermatology life quality index; UCT: urticaria control test. a. All patients with angioedema also had wheals in this study. b. Normal reference range: < 100 kU/L. IgE results were available for 128 patients. c. The cutoff value to determine an elevated total IgE level: ≥100 kU/L. IgE results were available for 128 patients. d. ASST results were available for 88 patients. e. Thyroid autoantibody levels were available for 105 patients*

were generated to compare the ratio of IgG-anti-TPO/IgE, IgG-anti-TPO and total IgE. The area under the curve (AUC) of the ROC value was calculated for the response evaluation of omalizumab treatment. ROC analyses were used to define cut-off points of IgG-anti-TPO/IgE, IgG-anti-TPO and total IgE to determine omalizumab response. A ***P*** value less than 0.05 was considered to indicate statistical significance.

RESULTS

Antihistamine-resistant CU patients show poor disease control at baseline

In total, 138 patients were included, and 63.0% (n = 87/138) of them had CSU only, 23.9% (n = 33/138) of them had CIndU only, 13.0% (n = 18/138) of them had both CSU and CIndU (Table 1). The majority of the patients were female (66.7%, n = 92/138), and the mean age was 39.6 ± 13.4 years (Table 1). The oldest patient was 84 years old. The median CU duration, assessed as the time from CU diagnosis to omalizumab initiation, was 24 months (IQR: 12–56 months). In total, 35.5% (n = 49/138) had a diagnosis of CU with angioedema at baseline (Table 1). The average omalizumab treatment period was 6.0 months (IQR: 4.0–11.0 months). All of the patients had a UCT<12 at baseline, indicative of uncontrolled disease, and the median baseline UCT was 3.0 (IQR: 0.0–4.0). Baseline DLQI was 18.0 (IQR:14.0–21.0), indicating a very large impact on patient QoL.

The median IgE level was 94.4 (48.9–309.0) kU/L, and 47.7% (n = 61/128) of patients had elevated (>100 kU/L) levels of IgE. Blood levels of antithyroid autoantibodies were elevated in 29 of 105 patients (27.6%). More than half of the patients (53.4%, n = 47/88) were autologous serum skin test (ASST)-positive.

Omalizumab treatment reduces the use of oral corticosteroids and immunosuppressive agents

Before commencing omalizumab treatment, all of the patients had received a higher than standard dosed second-generation H_1-antihistamine

Types of CU	N	Complete response	Partial response	Non-response
CSU	87	60 (69.0%)	15 (17.2%)	12 (13.8%)
CIndU	33	24 (72.7%)	6 (18.2%)	3 (9.1%)
SDerm	23	17 (73.9%)	5 (21.7%)	1 (4.3%)
ColdU	1	1 (100.0%)	0	0
CholU	8	5 (62.5%)	1 (12.5%)	2 (25.0%)
SDerm+ColdU	1	1 (100.0%)	0	0
CSU+CIndU	18	6 (33.3%)	9 (50.0%)	3 (16.7%)
CSU+SDerm	14	5 (35.7%)	7 (50.0%)	2 (14.3%)
CSU+ColdU	2	0	1 (50.0%)	1 (50.0%)
CSU+ColdU+HU	1	1 (100.0%)	0	0
CSU+SDerm+CholU	1	0	1 (100.0%)	0
Total	138	90 (65.2%)	30 (21.7%)	18 (13.1%)

Table 2. Response to omalizumab in patients with different types of urticaria *Abbreviations: CholU: cholinergic urticaria; CIndU: chronic inducible urticaria; ColdU: cold urticaria; CSU: chronic spontaneous urticaria; CU: chronic urticaria; HU: heat urticaria; SDerm: symptomatic dermographism*

(SGAH) or a combination of different SGAHs. Omalizumab treatment was administered concurrently with antihistamines in 74.6% (n = 103/138) of patients, among which nearly half (n = 50/103, 48.5%) of the patients received standard-dosed SGAHs, 18.4% (n = 19/103) received updosed SGAHs, and 33.0% (n = 34/103) were treated with a combination of different SGAHs.

Only very few patients used treatments other than antihistamines at the time when omalizumab therapy was started (traditional Chinese medicine: n = 15, methotrexate: n = 4, oral corticosteroid: n = 5, cyclosporine A: n = 5, antidepressant: n = 7).

Before omalizumab treatment, oral corticosteroids were used by 24.6% (n = 34/138) of patients, and the use of oral corticosteroids significantly decreased to 3.6% (n = 5/138) after commencing omalizumab (***P*** < 0.001). Similarly, the use of immunosuppressive agents (eg, azathioprine, cyclosporine A, methotrexate) also significantly decreased from 26.8% (n = 37/138) to 6.5% (n = 9/138) after initiating omalizumab (***P*** < 0.001). There were 35 (25.4%, n = 35/138) patients who received no other medication when omalizumab therapy was started.

Most of the CU patients benefit from omalizumab therapy

A total of 87.0% (n = 120/138) of the CU patients responded to omalizumab therapy, among which 65.2% (n = 90/138) of the patients showed complete response and 21.7% (n = 30/138) of the patients showed partial response (Table 2). Patients with CSU, CIndU, or both responded to omalizumab therapy in 86.2% (n = 75/87), 90.9% (n = 30/33) and 83.3% (n = 15/18) of cases, respectively (Table 2). The proportions of complete response in patients with CSU only (69.0%, n = 60/87) or CIndU only (72.7%, n = 24/33) were significantly higher (***P*** = 0.009) than that of patients with both CSU and CIndU (33.3%, n = 6/18). Meanwhile, the proportions of patients who achieved DLQI≤1 indicating no QoL impairment in patients with CSU only (74.7%, n = 65/87) or CIndU only (69.7%, n = 23/33) were also significantly higher (***P*** = 0.040) than that of patients with both CSU and CIndU (44.4%, n = 8/18). The improvements of UCT and DLQI at week 12 or throughout the treatment period were comparable between patients with CSU, CIndU and both (Table 3).

Before commencing omalizumab, all of the patients had uncontrolled CU (UCT score <12). During the first month of omalizumab treatment, 55.1% (n = 76/138) of the patients achieved well-controlled disease (defined as a UCT score ≥ 12; Fig. 1A). At the third month, a well-controlled disease status was achieved by 70.4% (n = 76/108) of the patients (Fig. 1A). The response rate continued to increase and maintained a high level during the treatment period (Fig. 1A). The UCT score significantly increased from 3.0 (IQR: 0.0–4.0) at

http://doi.org/10.1016/j.waojou.2020.100501

Outcomes	CSU (n = 87)	CIndU (n = 33)	CSU+CIndU (n = 18)	*P* value
Change from baseline to week 12 in UCT [a]	11.0 (7.0–13.0)	11.0 (9.0–12.5)	8.0 (4.8–11.3)	0.111
Change in UCT throughout treatment period	12.0 (10.0–15.0)	12.0 (9.0–14.0)	11.0 (9.8–12.0)	0.243
Patients achieved UCT ≥ 12, n (%)	75 (86.2)	30 (90.9)	15 (83.3)	0.756
Patients achieved UCT = 16, n (%)	60 (69.0)	24 (72.7)	6 (33.3)	**0.009**
Change from baseline to week 12 in DLQI [b]	11.5 (7.3–17.0)	14.0 (11.0–17.0)	11.5 (5.8–14.5)	0.442
Change in DLQI throughout treatment period	15.0 (11.0–20.0)	17.0 (13.0–20.5)	14.5 (10.8–20.3)	0.309
Patients achieved DLQI ≤ 1, n (%)	65 (74.7)	23 (69.7)	8 (44.4)	**0.040**

Table 3. Treatment outcomes with omalizumab in patients with different types of urticaria *Abbreviations: CIndU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; DLQI: dermatology life quality index; UCT: urticaria control test. The significance of bold indicates a P value < 0.05. a. UCT scores at week 12 were available for 73 patients with CSU, for 21 patients with CIndU, and for 14 patients with both CSU and CIndU. b. DLQI scores at week 12 were available for 72 patients with CSU, for 21 patients with CIndU, and for 14 patients with both CSU and CIndU*

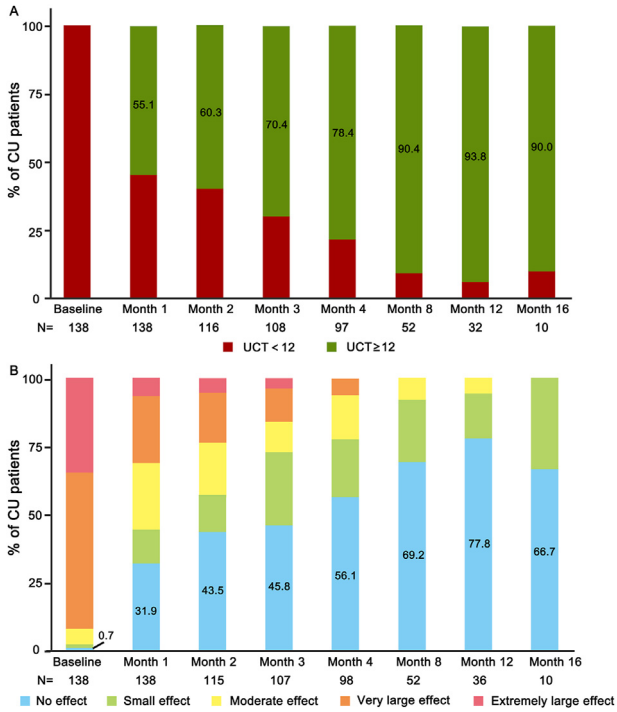

Fig. 1 A. The proportion of CU patients with uncontrolled (UCT<12) or controlled (UCT ≥ 12) disease. B. The proportion of CU patients with different QoL impairment status according to DLQI score. Abbreviations: CU: chronic urticaria; QoL: quality of life; UCT: urticaria control test

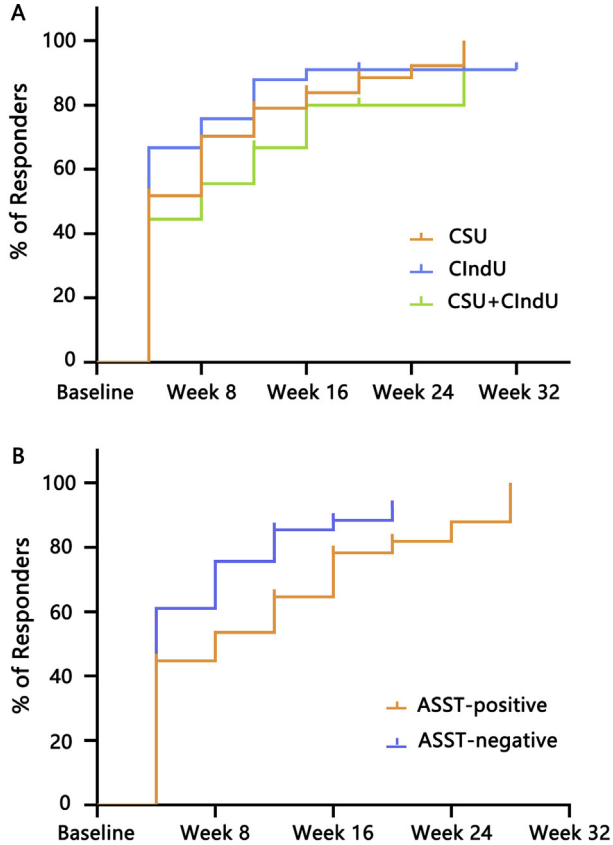

Fig. 2 A. The proportion of responders in patients with CSU, CIndU, or both during treatment period (n = 138). B. Kaplan-Meier curves showing the proportion of responders with positive and negative ASST over time. Abbreviations: ASST: autologous serum skin test; CSU: chronic spontaneous urticaria; CIndU: chronic inducible urticaria

Characteristics	Responders (n = 120)	Non-responders (n = 18)	*P* value
Demographic features			
Sex: female, n (%)	79 (65.8)	13 (72.2)	0.592
Age (y), mean ± SD	39.59 ± 13.41	39.83 ± 13.85	0.943
Clinical features			
Types of CU, n (%)			
CSU	75 (62.5)	12 (66.7)	0.760
CIndU	30 (25.0)	3 (16.7)	
CSU+CIndU	15 (12.5)	3 (16.7)	
Disease duration (mo), median (IQR)	24 (12–51)	39 (18–81)	0.084
Concomitant angioedema, n (%) [a]	39 (32.5)	10 (55.6)	0.057
Baseline UCT, median (IQR)	3.0 (1.0–4.8)	1.5 (0.0–3.0)	0.120
Baseline UAS7, median (IQR) [b]	28.0 (24.0–31.0)	30.0 (23.5–35.0)	0.249
Treatment period (mo), median (IQR)	6.0 (4.0–12.0)	4.5 (3.8–5.5)	**0.035**
Immunological features			
Total IgE (kU/L), median (IQR)	121.5 (62.5–320.3)	35.0 (12.7–86.5)	**<0.001**
Elevated total IgE, n (%)[c]	59 (53.6)	2 (11.1)	**0.001**
Low total IgE, n (%) [d]	16 (14.5)	11 (61.1)	**<0.001**
Elevated thyroid autoantibodies, n (%) [e]	20 (23.0)	9 (50.0)	**0.041**
Elevated IgG-anti-TPO, n (%) [f]	13 (14.9)	8 (44.4)	**0.012**
Elevated IgG-anti-TG, n (%) [g]	15 (17.2)	6 (33.3)	0.219
IgG-anti-TPO: total IgE, median (IQR)	0.09 (0.03–0.23)	1.22 (0.26–5.48)	**<0.001**
Positive ASST, n (%) [h]	39 (51.3)	8 (66.7)	0.322

Table 4. The demographic, clinical, and immunological features of responders and non-responders *Abbreviations: ASST: autologous serum skin test; CIndU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; IQR: interquartile range; SD: standard deviation; TG: thyroglobin; TPO: thyroid peroxidase; UAS7: urticaria activity score 7; UCT: urticaria control test. The significance of bold indicates a P value < 0.05. a. All patients with angioedema also had wheals in this study. b. Baseline UAS7 was available for 99 patients. c. The cutoff value to determine an elevated total IgE level: ≥ 100 kU/L. d. The cutoff value to determine a low total IgE level: < 40 kU/L. e. Thyroid autoantibody levels were available for 105 patients. f. Normal reference range for IgG-anti-TPO: 0–34 IU/ml. g. Normal reference range for IgG-anti-TG: 0–115 IU/ml. h. ASST results were available for 88 patients*

baseline to 12.0 (IQR: 6.8–15.0) at the first month (***P*** < 0.001), and achieved 14.0 (IQR: 10.3–16.0) at the third month. Patients' UCT scores continued to improve and retained a high level during the treatment period.

No prespecified dosing protocol was followed, and dosing varied in our study. The doses of omalizumab given to all patients are shown in Supplemental Figure 1. Initial doses chosen and adjustment of the dosage were based on disease activity and disease control status.

Time to respond to omalizumab therapy

Benefits of omalizumab treatment were evident early (soon after the first treatment before week 4) in most patients. However, the speed of onset of effect can vary among individuals.

The median time to respond to omalizumab therapy was 4, 4, and 8 weeks for patients with CSU only, CIndU only and for patients with both CSU and CIndU, respectively (Fig. 2A). The speed of onset of effects was comparable among patients with CSU, CIndU, or both (***P*** = 0.477; Fig. 2A).

The median time to achieve well-controlled urticaria was 8 and 4 weeks for patients with positive and negative ASST results, respectively (Fig. 2B). ASST-positive omalizumab responders are more likely to have a slow response to treatment compared with ASST-negative responders (***P*** = 0.043; Fig. 2B).

Omalizumab treatment results in substantial quality of life improvement

Omalizumab treatment led to a notable improvement in the QoL of patients as assessed by DLQI. Patients' median DLQI score significantly decreased from 18.0 (IQR:14.0–21.0) to 7.0 (IQR:1.0–12.3) during the first month of treatment (***P*** < 0.001), and it continued to decrease to 2.0 (IQR: 0.0–8.0) at the third month (***P*** < 0.001).

Characteristics	Relapsed (n = 29)	Non-relapsed (n = 14)	*P* value
Demographic features			
Sex: female, n (%)	19 (63.3)	11 (73.3)	0.502
Age (y), mean ± SD	40.07 ± 16.11	37.71 ± 11.47	0.627
Clinical features			
Types of CU, n (%)			
CSU	18 (62.1)	8 (53.3)	0.121
CIndU	7 (24.1)	6 (42.9)	
CSU+CIndU	4 (13.8)	0 (0.0)	
Disease duration (mo), median (IQR)	52.0 (17.0–96.0)	15.0 (11.8–24.0)	**0.007**
Concomitant angioedema, n (%)	10 (34.5)	5 (35.7)	1.000
Baseline UCT, median (IQR)	3.0 (1.5–4.0)	3.0 (0.8–4.3)	0.947
Baseline UAS7, median (IQR) [a]	30.0 (24.5–32.3)	26.5 (24.3–29.8)	0.311
Treatment period (mo), median (IQR)	12.0 (6.5–13.5)	10.5 (7.8–12.3)	0.548
Immunological features			
Total IgE (kU/L), median (IQR) [b]	179.9 (75.9–468.5)	72.5 (51.3–109.5)	**0.020**
Elevated total IgE, n (%) [c]	19 (65.5)	3 (21.4)	**0.007**
Low total IgE, n (%) [d]	2 (6.9)	2 (14.3)	0.825
Elevated thyroid autoantibodies, n (%) [e]	6 (26.1)	0 (0.0)	0.290
IgG-anti-TPO: total IgE, median (IQR)	0.07 (0.03–0.47)	0.18 (0.17–0.23)	0.201
Positive ASST, n (%) [f]	10 (47.6)	5 (45.5)	0.907

Table 5. Comparison of the clinical features and laboratory results between patients with and without disease relapse. *Abbreviations: ASST: autologous serum skin test; CIndU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; IQR: interquartile range; SD: standard deviation; TG: thyroglobin; TPO: thyroid peroxidase; UAS7: urticaria activity score 7; UCT: urticaria control test. The significance of bold indicates a P value < 0.05. a. Baseline UAS7 was available for 31 patients. b. Normal reference range: < 100 kU/L. c. The cutoff value to determine an elevated total IgE level: ≥ 100 kU/L. d. The cutoff value to determine a low total IgE level: < 40 kU/L. e. Thyroid autoantibody levels (including IgG-anti-TPO and IgG-anti-TG) were available for 30 patients. Normal reference range for IgG-anti-TPO: 0–34 IU/ml. Normal reference range for IgG-anti-TG: 0–115 IU/ml. f. ASST results were available for 32 patients.*

Patients' median DLQI score could achieve 1.0 (IQR: 0.0–4.0) at the end of the treatment period. The median DLQI improvement was 15.0 (IQR: 11.0–20.0), which decreased by 83.7% compared to baseline.

As assessed by DLQI, before commencing omalizumab, CU showed an extremely large impact and a very large impact on the lives of 34.8% (n = 48/138) and 57.2% (n = 79/138) of patients, respectively (Fig. 1B). After the first month of treatment, the percentage of patients suffering from an extremely large and very large impact on QoL dropped markedly, to 6.5% (n = 9/138) and to 24.6% (34/138), respectively (Fig. 1B). For the first month of treatment, 31.9% (n = 44/138) of patients reported to have no QoL impairment (Fig. 1B). Low levels of QoL impairment were maintained during the treatment period.

Omalizumab non-responders have unique immunological features and shorter treatment periods

There were 18 patients (13.1%, n = 18/138) who did not respond to omalizumab during the treatment period. Non-responders had some unique immunological features (Table 4) including lower baseline total IgE levels (35.0 vs. 121.5 kU/L, ***P*** < 0.001). The proportion of non-responders with elevated total IgE levels was markedly lower than that of responders (11.1% vs. 53.6%, ***P*** = 0.001); the rate of patients with low total IgE levels was significantly higher in non-responders than responders (61.1% vs. 14.5%, ***P*** < 0.001). Also, more non-responders than responders had elevated thyroid autoantibodies (50.0% vs. 23.0%, ***P*** = 0.041). The proportion of patients with elevated IgG-anti-TPO was significantly higher in

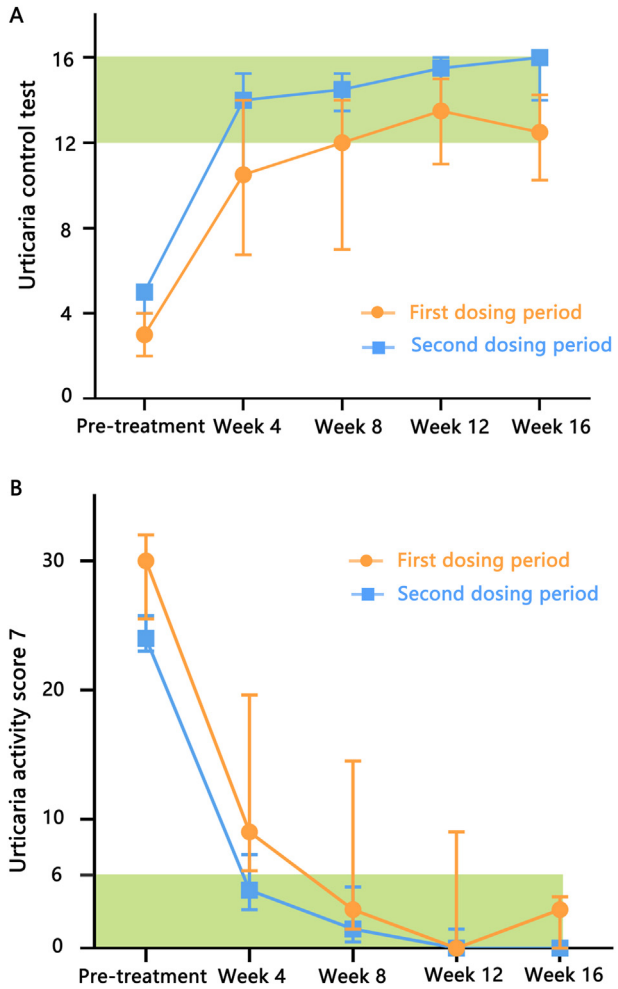

Fig. 3 A. UCT scores in patients re-treated with omalizumab (n = 10). B. UAS7 scores in patients re-treated with omalizumab (n = 9). Abbreviations: UAS7: urticaria activity score 7; UCT: urticaria control test

non-responders than in responders (44.4% vs. 14.9%, ***P*** = 0.012). As determined by ROC analyses (area under the curve), the most significant difference between non-responders and responders was in their median ratio of serum IgG-anti-TPO to serum total IgE (1.22 vs. 0.09, ***P*** < 0.001; Supplemental Fig. 2 and Supplemental Table 2). And rates of patients with ratios higher than 0.24 also showed significant difference between responders and non-responders (23.8% vs. 77.8%, ***P*** < 0.001).

Non-responders also had shorter treatment durations (4.5 vs. 6.0 months, ***P*** = 0.035) compared with responders (Table 4). There was no significant difference between non-responders and responders in terms of demographic features, types of urticaria, disease duration, concomitant angioedema, baseline UCT and UAS7 score, positivity for autologous serum skin test (ASST) or IgG-anti-TG (Table 4). The response rate showed no major difference between patients with and without angioedema (79.6% vs. 91.0%, ***P*** = 0.057).

CU patients who relapse after omalizumab discontinuation have higher total IgE levels and longer disease duration

We discontinued omalizumab therapy in 43 patients with CU who showed complete response defined as UCT = 16 during the period of omalizumab treatment. Their median treatment duration was 12.0 (IQR: 7.0–13.0) months. The strategies of omalizumab discontinuation in these patients are presented in Supplemental Table 1.

Two of 3 patients (67.4%, n = 29/43) experienced a relapse despite continued antihistamine treatment within 3–16 weeks after their last omalizumab injection. The median relapse time was 9.0 weeks (95%CI: 6.5–11.5 weeks). The other 14 patients had sustained well-controlled disease for a minimum of 12 weeks and up to 14 months (the duration of the study period) after their last omalizumab injection.

Patients with disease relapse had higher baseline total IgE levels (179.9 vs 72.5 kU/L, ***P*** = 0.020) and longer disease duration (52.0 vs 15.0 months, ***P*** = 0.007) than patients without disease relapse (Table 5). Demographic features, types of urticaria, concomitant angioedema, baseline UCT and UAS7 scores, treatment period, patients with elevated thyroid autoantibodies, the ratio of IgG-anti-TPO to total IgE, or positivity for ASST did not significantly differ between patients with or without relapse (Table 5).

Retreatment with omalizumab results in rapid remission

We reinitiated omalizumab treatment in 10 patients who experienced relapse, all patients reported a rapid response after the first injection within the first 4 weeks of retreatment.

Patients' median UCT score before retreatment was 5.0 (IQR: 4.0-5.3) and significantly increased to 14.0 (IQR: 10.5–15.3) after the first injection of retreatment (***P*** = 0.005), and maintained at a high level during the retreatment period (Fig. 3A). All

patients regained control of symptoms (defined as UCT $\geq$ 12) after the third injection of retreatment.

Nine of the 10 patients who received retreatment had CSU, and their median UAS7 score was 24.0 (IQR: 23.0–25.8) before retreatment. These patients reported a significant decrease of their UAS7 score to 4.5 (IQR: 3.0–7.3) after the first injection of retreatment ($P = 0.008$), and they maintained a low level of disease activity during the retreatment period (Fig. 3B).

Omalizumab was well tolerated

During the study period, 138 patients received a total of more than 1000 treatments, and the longest treatment duration was 22 months. Adverse events reported were of mild-to-moderate intensity. No deaths or anaphylaxis was reported.

However, 11 patients (8.0%, n = 11/138) experienced flare up of their urticaria after the first or the second injection of omalizumab. None of them reported extracutaneous signs or symptoms (eg, hypotension, tachycardia, dyspnea, oxygen desaturation, nausea, vomiting). Seven of them discontinued omalizumab due to ineffectiveness.

Eight patients reported injection site reactions (eg, warmth, erythema, itching) after omalizumab treatment. One patient experienced headache and dizziness after the first treatment.

DISCUSSION

This study is the first to confirm, in Chinese patients with CSU, CIndU, or both, the efficacy of omalizumab in controlling CU signs and symptoms and in improving QoL.

Patient demographics and clinical characteristics in this study are representative of the general population of patients with CU. The arduous course of treatment for these difficult-to-treat patients with CU was confirmed by the long periods of time from diagnosis to omalizumab treatment initiation which was 24 months (IQR: 12–56 months). Treatments used prior to commencing and in combination with omalizumab did not always adhere to guidelines. Omalizumab could markedly reduce the usage of oral corticosteroids ($P < 0.001$) and immunosuppressive agents ($P < 0.001$); and reduce the dosage of SGAHs used.

A total of 87.0% (n = 120/138) of the CU patients responded to omalizumab therapy, among which 65.2% (n = 90/138) of the patients showed complete response. These numbers were somewhat higher than those observed in the randomized controlled phase III trials of CSU,[7-9] but are very much in accordance with the results of other real-life studies.[11,18,19] Kocaturk E et al reported a total response rate of 76.1% and 83.3% in CIndU and CSU respectively in real-life clinical settings.[20] And Cherrez-Ojeda I et al reported a response rate of 80.0% in CU patients treated with omalizumab in Latin America.[18] For CSU, an average complete response rate of 72.2% (95% CI: 66.1%–78.3%) was reported by Tharp M et al in a meta-analysis of real-world evidence including 45 real-world studies; and an additional average partial response rate of 17.8% (95%CI: 11.7%–23.9%) was reported by the same meta-analysis.[12]

CU has a detrimental impact on many aspects of patient QoL. Omalizumab can significantly improve patient QoL as assessed by DLQI. Improvement of DLQI score after omalizumab treatment ranges from 57.1% to 100.0%, and the change of DLQI score at the end of treatment compared to baseline was 9.6–18.5 in previous real-life studies.[21–25] The decrease of DLQI score in our study was in compliance with the results of other studies. Low levels of QoL impairment were maintained throughout the treatment period in our study.

Another finding is that patients with both CSU and CIndU simultaneously can also benefit from omalizumab therapy. The improvements of UCT and DLQI score at week 12 or throughout the treatment period were comparable between patients with CSU, CIndU, and both. In 10%–50% of patients, CSU occurs in combination with CIndU.[26] Patients who have CSU with comorbid CIndU were excluded from the omalizumab phase III trials and several other RCTs. However, comorbidity of CIndU is thought to be linked to longer disease duration and higher disease activity.[26]

In our study, 83.3% (n = 15/18) of the patients with CSU plus CIndU benefited from omalizumab therapy, among which 33.3% (n = 6/18) of them

showed complete response. In a retrospective study, Metz M and coworkers reported 5 patients with CSU plus delayed pressure urticaria and 1 patient with CSU plus SD had complete symptom control after the first use of omalizumab.[27] In another report, a woman with CSU plus pressure urticaria plus symptomatic dermographism experienced complete remission of her 3 urticarias after the first injection of omalizumab. Autoallergy has been postulated to be a cause of CIndU, the appropriate trigger (eg, friction, cold, heat, pressure, sunlight, passive warming/exercise) may result in *de novo* synthesized autoantigen, which is detected by IgE autoantibodies, resulting in mast cell degranulation.[28,29] Omalizumab blocks binding of IgE to FcεRI, therefore, it can intervene in this common pathway and block the mast cell-activating signal so as to improve the symptoms of both CSU and CIndU simultaneously.[6]

However, the complete response rate, as well as the proportion of patients who achieved a DLQI score $\leq$1, indicating no impairment of QoL, were significantly lower in patients with both CSU and CIndU in our study. We speculate that in patients with both CSU and CIndU, longer treatment duration and higher dosage can result in better therapeutic effect. Based on the findings of phase III clinical trials in CSU, some patients who had not met the definitions of complete response at primary endpoint at week 12 met those definitions with continued dosing at week 24: ASTERIA I (26%, 39%, and 55%, respectively, of the 75-, 150-, and 300-mg arms) and GLACIAL (49% in the 300-mg omalizumab arm).[30] Although the international guideline recommends 300 mg/4 weeks of omalizumab as standard dose,[2] increasing real-world studies demonstrate that omalizumab updosing could be effective in partial responder or non-responder patients with CU. For example, Curto-Barredo and coworkers reported that 43 and 16 of the 79 previously partial responder or non-responder patients became responders after updosing to 450 and 600 mg/4 weeks, respectively.[31]

Our study also suggested that a positive ASST might predict a slow response to omalizumab. ASST was easy to perform clinically and was designed to identify serum IgG autoantibodies to FcεRI/IgE. In CU patients with IgG autoantibodies against IgE or FcεRI, the effect of omalizumab might be associated with the decrease in mast cell–bound IgE levels and the subsequent down-regulation of FcεRI on mast cells and basophils.[5] Thus patients with IgG autoantibodies against IgE or FcεRI can be expected to show a slow response to omalizumab treatment. The finding of our study was consistent with the study from Nettis E et al and Gericke J et al.[32,33]

Non-responders in our study had higher rates of low IgE, elevated IgG-anti-TPO, and high ratios of IgG-anti-TPO to total IgE, all them being biomarkers for autoimmune chronic urticaria as demonstrated by the PURIST study.[34] Therefore, we have good reason to speculate that CU patients with an autoimmune basis may respond differently to omalizumab. The pathogenesis of autoimmune chronic urticaria involves IgG autoantibodies to IgE or its high-affinity receptor FcεRI. Autoimmunity might be linked to delayed response as mentioned above and we may therefore infer that some of the "non-responders" are likely to respond if they continued their omalizumab therapy.[33] The fact that responders tend to have longer treatment periods in our study supports this notion.

Relapse rates after ceasing omalizumab are high in clinical trials and in real life, ranging from 17.6% to 67%.[32,35–40] The OPTIMA study revealed a 44.4%–50.0% relapse rate after 6 months of omalizumab treatment.[10] The XTEND-CIU study showed a relapse rate of 43.4% and 45.1% during the 12 weeks after discontinuation of omalizumab in patients treated for either 24 or 48 weeks.[36] The relapse rate in our study was 67.4% (n = 29/43). We found that patients with relapse had longer disease durations and higher baseline total IgE levels than that of patients without relapse.

There was no rebound phenomenon after discontinuation of omalizumab in our study. The median UCT and UAS7 score before the second dosing period were comparable with the first dosing period. Basically, omalizumab is not a curative or disease-modifying treatment. Therefore, instead of treating patients for a fixed length of period, omalizumab should be used until the disease is gone. Insufficient duration of treatment might result in avoidable flare ups of urticaria. All relapsed patients who underwent retreatment

were able to regain symptom control with a second course of treatment in our study indicating that retreatment with omalizumab is an effective therapy option for patients who previously benefited from this drug.

Generally, omalizumab is a safe and well tolerated treatment. Adverse events reported were of mild-to-moderate intensity in our study. Clinical trials have shown that omalizumab was well tolerated in CSU patients older than 12 years old.[7–9] However, we observed exacerbation of urticaria in 11 patients after the first or the second injection. Ertaş R et al also reported 4 patients who experienced flare up of urticaria during omalizumab administration, which led to discontinuation of the drug.[41] In our study, exacerbation of urticaria did not occur again during the remainder of the treatment period.

Potential limitations of the present study are its retrospective design and the likelihood of patients lost to follow-up. Moreover, since the data were collected at a single specialized urticaria center, the results might not represent the general CU population in China due to limited numbers. Our study did not include CU patients with angioedema only, and the efficacy of omalizumab for angioedema was not systematically studied. Further studies should assess the effects of omalizumab on angioedema in CU patients with the help of validated tools and include CU patients who have angioedema but no wheals.

In conclusion, our study indicates that omalizumab is highly effective and safe in patients with antihistamine-resistant CSU, CIndU or both. A total of 87.0% of the CU patients benefited from omalizumab treatment. The therapeutic effect and speed of onset of effect for omalizumab were comparable among patients with CSU, CIndU or both. ASST-positive patients were more likely to show a slow response to omalizumab therapy. Non-responders tend to have lower baseline total IgE levels, higher proportions of elevated IgG-anti-TPO, higher ratios of IgG-anti-TPO to total IgE and shorter treatment periods. Patients with higher baseline total IgE levels and longer disease durations are more likely to experience rapid relapse after discontinuation of omalizumab. However, omalizumab retreatment was an effective therapy option for those who had previously benefited from this drug.

Abbreviations

ASST, autologous serum skin test; AUC, area under the curve; CholU, cholinergic urticaria; CIndU, chronic inducible urticaria; ColdU, cold urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; DLQI, dermatology life quality index; HU, heat urticaria; IgE, immunoglobulin E; IQR, interquartile range; QoL, quality of life; ROC, receiver-operator characteristic; SD, standard deviation; SDerm, symptomatic dermographism; SGAHs, second-generation H_1-antihistamines; TG, thyroglobin; TPO, thyroid peroxidase; UAS7, urticaria activity score 7; UCARE, Urticaria Center of Reference and Excellence; UCT, urticaria control test.

Author contributions

Yudi Chen: substantial contributions to acquisition, analysis and interpretation of data; drafted the manuscript;
Miao Yu: substantial contributions to acquisition of data; drafted the article;
Xiaojie Huang: conception and design of the study; revising the manuscript critically for important intellectual content;
Ping Tu: substantial contributions to conception and study design; revising the manuscript critically for important intellectual content;
Peikun Shi: substantial contributions to acquisition of data; reviewed the article;
Marcus Maurer: substantial contributions to conception and study design; reviewed the article critically for important intellectual content;
Zuotao Zhao: substantial contributions to conception and study design; reviewed the article critically for important intellectual content.

Funding source

This study was funded by the Joint Sino-German Research Project of National Natural Science Foundation of China (grant no. GZ901).

Availability of data and materials

The datasets are available on ResMan (http://www.medresman.org.cn/uc/index.aspx).

Ethics approval

The study was approved by China Ethics Committee of Registering Clinical Trial (ChiECRCT20190131).

Trial registration number

The study was registered with the Chinese clinical trial registry (ChiCTR2000038085).

Consent for publication
The submission of the article and the publication of the article by World Allergy Organization Journal has been approved by all authors. And its publication has been approved by the responsible authorities at the institution where the work is carried out.

Submission declaration
We confirm that the manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Declaration of competing interest
Yudi Chen: none;
Miao Yu: none;
Xiaojie Huang: none;
Ping Tu: none;
Peikun Shi: none;
Marcus Maurer: Speaker and/or advisor and recipient of institutional research funding from Genentech and Novartis;
Zuotao Zhao: research support from Novartis outside the submitted work.

Acknowledgments
We acknowledge the support of the GA^{2}LEN network of Urticaria Centers of Reference and Excellence (UCAREs; www.ga2len-ucare.com). We thank Zhi-Yue Chu, Jia Yu, Bo Liu, and Xiao-Ting Song for assistance with patient follow-ups and data collection.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2020.100501.

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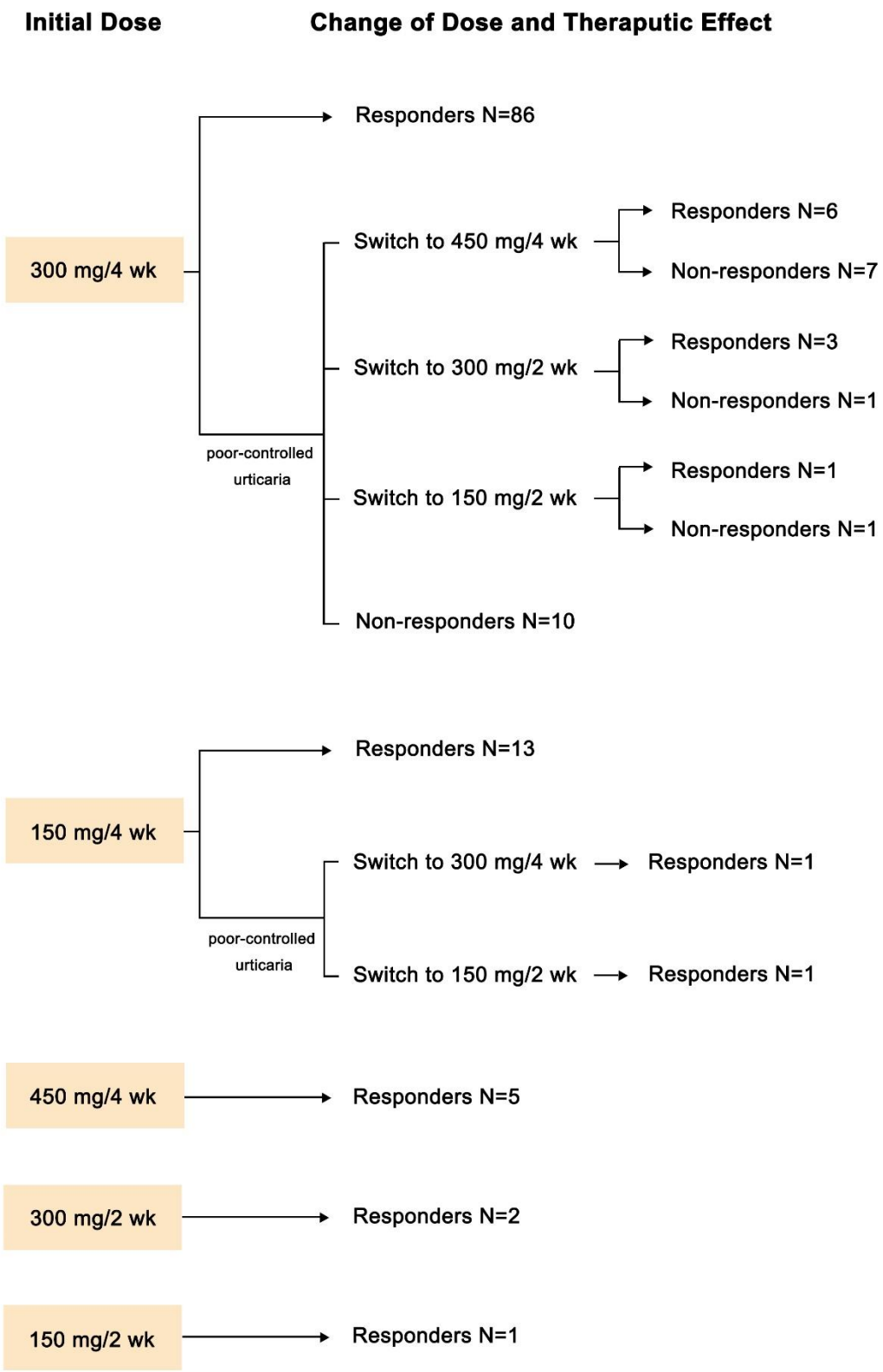
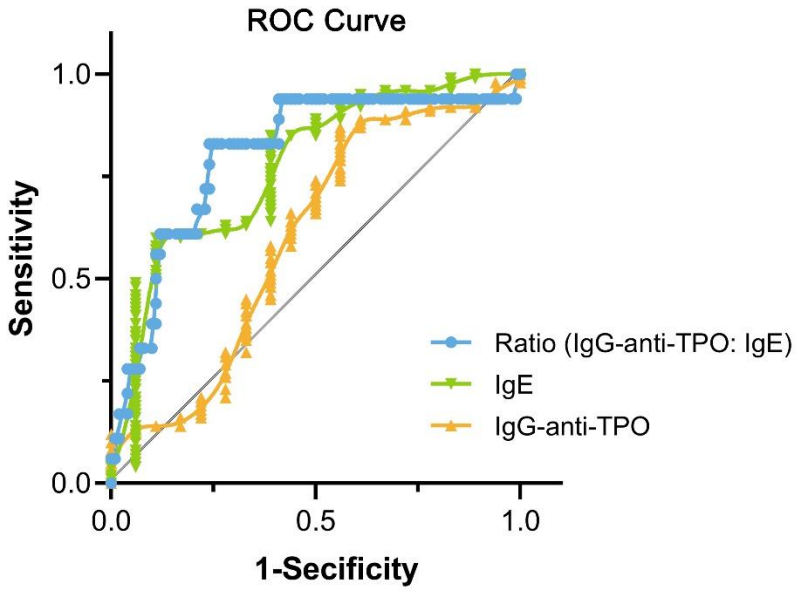
Supplemental Figures

Supplemental Fig 1. A flowchart of the doses of omalizumab during the study period (N=138).



Supplemental Fig 2. As determined by ROC analyses (area under the curve), the IgG-anti-TPO:IgE ratio is the best predictor of response to omalizumab, followed by IgE and IgG-anti-TPO (N=138). Abbreviations: ROC: receiver operating characteristic; TPO: thyroid peroxidase.



Supplemental Tables

Supplemental Table 1. Effective dose of omalizumab to cause complete relief of symptoms and strategies of discontinuation (N=43).

Effective dose	Drug discontinuation strategies	Number of patients
300 mg/ 4 wk	Stop treatment all at once	14
	Downdose to 150 mg/4 wk	14
150 mg/4 wk	Stop treatment all at once	6
450 mg/4 wk	Downdose to 300 mg/4 wk and 150 mg/4 wk	4
300 mg/2 wk	Increase interval to 300 mg/4 wk and then stop treatment	3
150 mg/2 wk	Increase interval to 150 mg/4 wk and then stop treatment	2

Supplemental Table 2. The ROC analyses of prediction of response to omalizumab based on IgG-anti-TPO, IgE, and ratio of IgG-anti-TPO/IgE. Abbreviations: AUC: area under the curve; CI: confidence interval; ROC, receiver operating characteristic; IgE, immunoglobulin E.

	IgG-anti-TPO (Cut off=39.36) (95% CI)	**IgE** (Cut off=92.0) (95% CI)	**Ratio (IgG-anti-TPO: IgE)** (Cut off=0.24) (95%CI)	***P*** IgG-anti-TPO vs IgE	***P*** IgG-anti-TPO vs Ratio	***P*** IgE vs Ratio
AUC	0.60 (0.44-0.76)	0.77(0.65-0.90)	0.81(0.69-0.93)	0.100	**0.006**	0.396
Sensitivity	0.53 (0.06-0.97)	0.55(0.04-0.98)	0.75(0.12-0.94)	**<0.001**	**<0.001**	**0.001**
Specificity	0.57 (0.06-1.00)	0.73(0.17-0.94)	0.56(0.04-0.98)	**0.010**	0.710	**0.001**