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Omalizumab in children and adolescents with chronic urticaria: A 16 week real-world study

To the editor,

Omalizumab (Xolair®) is a recombinant humanized monoclonal anti-IgE antibody, which binds to free IgE, lowers free IgE levels and causes FcεRI receptors on basophils and mast cells to be downregulated.¹ Omalizumab is the first drug approved as an add-on therapy for patients (≥12 years old) with antihistamine-resistant chronic spontaneous urticaria (CSU). It is not approved for CSU patients younger than 12 years or patients with other forms of chronic urticaria (CU).² The information on the efficacy and safety of omalizumab in the management of pediatric CU is scarce.

We conducted a retrospective, observational real-world study to investigate the efficacy and safety of omalizumab in children and adolescents with antihistamine-resistant CU. Twelve patients aged < 18 years with antihistamine-resistant CU were treated with 150 or 300 mg of omalizumab every four weeks. A summary of the patients' baseline characteristics and dosage regimens are presented in Table 1. We used the urticaria control test (UCT) to assess disease

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control status, the children's dermatology life quality index (CDLQI) to evaluate quality of life impairment, at baseline and each visit, and monitored adverse events to assess safety. CU is classified, based on UCT scores in adults, as poorly controlled (UCT<12 points), well controlled ($12 \leq \text{UCT} < 16$ points) and completely controlled (UCT=16 points). A CDLQI score of 19–30, 13–18, 7–12, 2–6 and 0–1 indicate extremely large, very large, moderate, small and no impairment of patients' QoL, respectively. All 12 patients completed four months of treatment.

Two thirds (67%) of the patients achieved well-or-completely controlled CU (defined as a UCT score ≥ 12) after the first administration. The UCT score significantly increased from 2.5 (0.0-5.8) at baseline to 12.0 (1.3-13.8) after four weeks ($Z=-3.063$, $P=0.002$) and 15.0 (13.5-16.0) after 16 weeks ($Z=-3.065$, $P=0.002$). Patients with well-or-completely controlled disease ($n=8$) versus poorly controlled disease ($n=4$) at week four did not differ in terms of gender, age at onset, disease duration, or IgE levels, UCT scores and QoL impairment at baseline (Table S2). Both of the two patients with cholinergic urticaria did not achieve well controlled disease after the first administration of omalizumab, one did so after the second administration, and the other after the third administration. The beneficial effects of omalizumab in patients with symptomatic dermographism, cold urticaria, and solar urticaria were rapid, all achieved well-or-completely controlled disease after the first administration. The CDLQI score decreased from 17.5 (14.5-20.5) at baseline to 9.0 (3.0-13.8) after four weeks ($Z=-2.984$, $P=0.003$) and 2.0 (0.0-6.8) after 16 weeks ($Z=-3.063$, $P=0.002$). No adverse events were observed (Table S1). UCT and CDLQI scores at each visit are shown in Figure 1.

Our study confirmed the findings of previous case reports³, i.e. that omalizumab markedly, reliably and quickly reduced CU disease activity and impact in the pediatric age group, which was also similar to what has been described in adult CU patients.⁴⁻⁶ In line with our findings, a recent review of children with CU younger than 12 years reported that omalizumab achieved a complete response in 81% and a partial response in 19% of patients, without non-responders.⁷ In our study, omalizumab controlled CU symptoms in children and adolescents rapidly, with two thirds of patients achieving well-or-completely controlled disease after the first administration. The mechanisms of the rapid onset of effects were not entirely understood but were likely to

include the reduction of IgE autoantibodies against autoantigens.¹ Our study failed to find any predictors of early treatment response as adult patients, i.e., total IgE, BHRA and ASST results, which most likely because of the small number of patients.⁸

The study was the first real-world study on omalizumab treatment in children and adolescents with CU. Omalizumab is a promising but off label treatment option for children under the age of 12 with antihistamine-refractory CU. Further studies should be performed to obtain regulatory approval for its use in this age group. The limitations of this study included its small sample size, retrospective analyses of data, the relatively short follow-up time and the limited laboratory testing items. Also, the UCT is not formally validated for children.

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CONFLICTS OF INTEREST

Dr. Zhao is or recently was a speaker/advisor for and/or has received research funding from Novartis, Pfizer, Astellas, Galderma, Janssen, GSK, BAYER, LEO, MEDA Pharma and ALK Pharma, outside the submitted work.

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The rest of the authors declare that they have no relevant conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table 1. Demographic and clinical data of patients included in our study

N	Sex/age (years)	Age at onset (years)	IgE (IU/mL)	ASST	Count of periphera l basophils (10 ⁹ /L)	Type of urticaria	UCT	CDLQI	Doses, mg/ Interval, weeks
1	F/6	3	1456.2	Positive	0.00	CSU+SDer	5	17	150/4
2	M/5	1	72.6	Negative	0.00	CSU	6	12	150/4
3	F/14	11	352.0	Negative	0.00	CSU	5	19	150/4
4	F/12	10	106.9	-	0.01	CSU	0	24	150/4
5	M/12	11	300.0	Negative	0.02	CSU+SDer +CholU	8	14	150/4
6	M/16	14	34.2	Negative	0.01	CSU	7	10	300/4
7	M/3	2	15.2	-	0.00	CSU	0	23	150/4
8	F/11	10	821.0	-	0.01	SDer	3	21	150/4
9	F/5	3	98.0	Negative	0.00	ColdU	2	17	150/4
10	M/16	15	213.0	Negative	0.02	CholU	0	18	300/4→ 150/4
11	F/12	11	498.0	Negative	0.00	CSU	0	18	150/4
12	F/10	4	768.0	Negative	0.01	Solar urticaria	1	16	150/4
Total:	Total:	Mean±SD:	Median (IQR):	ASST (+):			Median (IQR):	Median (IQR):	
n=12	7F,5M	7.9±5.0	256.5(79.0-700.5)	n=1			2.5(0.0-5.8)	17.5(14.5-20.5)	

Abbreviations: ASST, autologous serum skin test; UCT, urticaria control test; CDLQI, children’s dermatology life quality index; CSU: chronic spontaneous urticaria; SDer: symptomatic dermographism; CholU: cholinergic urticaria

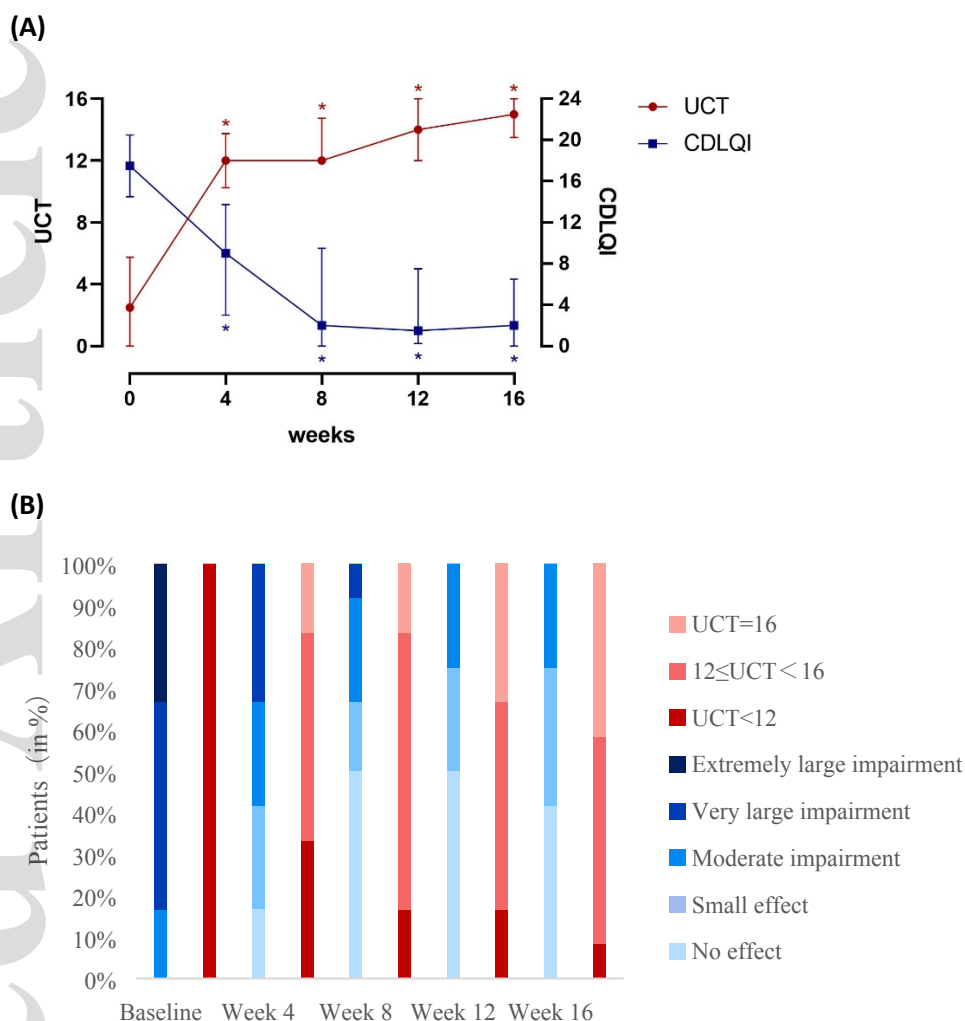


Figure 1 UCT and CDLQI score.

A. The median of UCT and CDLQI at each visit. Data are expressed as interquartile range with median.

Applications of omalizumab 150mg or 300 mg every four weeks notably and rapidly improve the disease control and QoL in CU patients as assessed by urticaria control test (UCT) and children's dermatology life quality index (CDLQI). In contrast with baseline, increases in UCT scores and decreases in CDLQI scores were significant statistically at each visit (Wilcoxon Matched-Pairs Signed-Ranks Test, $P < 0.05$).

B. The proportion of CU patients with different controlled disease and impact of QoL. Twelve patients all completed 16 weeks of omalizumab treatment. One case gained a satisfactory response at first and then experienced notable fluctuations, which was exactly the only one whose UCT was 11, below 12.

Abbreviations: UCT, urticaria control test; CDLQI, children's dermatology life quality index; CU, chronic urticaria

* $P < 0.05$ (Wilcoxon test) compared to week 0.

Online Supporting Information

Patients and study conduct

This retrospective, observational real-world study was conducted at the Department of Dermatology, Peking University First Hospital, Beijing, China. Data were collected between February 2018 and May 2020. The study was approved by the ethics committee of Chinese Ethics Committee of Registering Clinical Trial (ChiECRCT20190131) and registered with the Chinese clinical trial registry (ChiCTR1900024869). All patients provided informed consent.

Patients had to meet the following inclusion criteria: (1) Diagnosis of CU based on medical history, clinical photographs and provocation tests (for chronic inducible urticaria); (2) age of < 18 years; (3) poorly controlled disease defined as UCT < 12; (4) unresponsive (UCT < 12) to an oral H1- antihistamines at up to four times the licensed dose. Patients were excluded if they were participating in any clinical trials for CU or on omalizumab treatment for any other indications. Provocation tests and the determination of trigger thresholds were performed using FricTest® (Moxie, Berlin, Germany) for symptomatic dermographism (SDerm), TempTest® (Courage and Khazaka, Cologne, Germany) for Cold Urticaria (ColdU) and heat urticaria, and exercise provocation tests for cholinergic urticaria (CholU). Autologous serum skin testing (ASST) was conducted to detect autoreactivity¹. Total IgE levels were measured by a chemiluminescent immunoassay (ImmunoCAP; ThermoFisher Scientific, Sweden) before treatment.

Efficacy assessment

Patients were assessed for disease control and impact at the first and every follow up visit by use of the Urticaria Control Test (UCT) and the Children's dermatology life quality index (CDLQI), respectively.

The UCT retrospectively assesses the overall control of urticaria during the past four weeks with a total of four question, each with five answer options (scored with 0-4 points)². The UCT score is the sum of the scores of all four individual item scores (0-16 points). The lower the total score, the worse the disease control and the higher the

disease activity. CU is classified, based on UCT scores, as poorly controlled (UCT<12 points), well controlled (12≤UCT<16 points) and completely controlled (UCT=16 points). The minimal UCT change that can be considered as clinically relevant is 3 points³. For patients under 6 years old, the UCT was completed by the parents, patients over 6 years of age did this themselves.

The CDLQI has 10 questions and its score is calculated by summing the scores of the 10 answers, with a minimum of 0 and a maximum of 30. The higher the score, the greater the degree of impairment on patients' QoL. A CDLQI of 19–30 indicate extremely large impairment of patients' QoL, 13–18 denotes very large impairment, 7–12 means moderate impairment, 2–6 implies small effects on patients' QoL, and 0–1 marks no effect at all on patients' life.

Statistical analysis

Statistical analyses of the data were performed using the software SPSS 23.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA). Descriptive statistical analyses were performed, and data were shown as median (interquartile range, IQR), mean ± standard deviation (SD), or number (percentage). The Shapiro–Wilk test and histogram analyses were used to determine whether continuous variables were normally distributed. For the analysis of clinical outcomes (UCT and CDLQI), a paired Student's t-test and Wilcoxon Matched-Pairs Signed-Ranks Test was applied for normally and non-normally distributed data, respectively. A p value < 0.05 was considered to indicate statistically significant differences.

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Table S1. Dosage regimens and clinical response to omalizumab treatment

N	Disease duration (months)	Doses, mg/Interval, weeks	Combined medicine	Adverse events	Efficacy
1	38	150/4	None	None	Effective
2	52	150/4	Cetirizine	None	Effective
3	36	150/4	None	None	Effective
4	24	150/4	Cetirizine	None	Effective
5	13	150/4	Cetirizine	None	Effective
6	21	300/4	None	None	Effective
7	12	150/4	None	None	Effective
8	8	150/4	None	None	Effective
9	24	150/4	Cetirizine	None	Effective
10	11	300/4→150/4	None	None	Effective
11	7	150/4	None	None	Effective
12	72	150/4	Cetirizine	None	Effective

Table S2. Univariate analysis on disease control at 1st administration

	Well-controlled at the 1st administration (n=8)	Poor-controlled at the 1st administration (n=4)	P value
Female, n (%)	6 (75%)	1 (25%)	0.22 ***
Disease duration (months)	30.7±22.3	18.0±12.0	0.32**
Total IgE (IU/mL)	302.4 (79.0-807.8)	256.5 (64.7-339.0)	0.50*
Age at onset (years)	7.0±4.8	9.8±5.5	0.39**
Baseline UCT	2.5(0.3-5.8)	2.5(0-7.3)	0.93*
Baseline CDLQI	17.0(13.0-20.3)	18.5(15.0-22.0)	0.44*

***Fisher's Exact Test

**t-test

*Mann-Whitney U test