

Omalizumab in chronic inducible urticaria: A real-life study of efficacy, safety, predictors of treatment outcome and time to response

To the Editor,

Chronic inducible urticaria (CIndU) is characterized by wheals, angioedema or both in response to specific and definite triggers.¹ Half of CIndU patients are refractory to H₁-antihistamine treatment even at higher doses.² Multiple studies have proven the benefits of omalizumab in chronic spontaneous urticaria.³ Real-life data on the efficacy and safety of omalizumab treatment in CIndU are limited.^{4,5}

To explore the effects and features of complete and fast response of omalizumab treatment in CIndU, we performed a retrospective observational study at our Urticaria Center of Reference and Excellence (UCARE) between February 2018 and September 2020. All patients provided informed consent before entering the study. The study was conducted according to the Declaration of Helsinki. It was approved by the Chinese Ethics Committee of Registering Clinical Trial (ChiECRCT20190131) and registered with the Chinese clinical trial registry (ChiCTR1900024869). To be started on omalizumab therapy, patients had to be both adults (>18 years) and unresponsive to second-generation H₁-antihistamines. Patients were excluded if they were treated with omalizumab for any other indication (eg allergic asthma, allergic rhinitis). The diagnosis of CIndU was based on patient history, clinical picture and specific provocation tests.

We included 59 patients with CIndU, most had SD ($n = 41$, 69.5%, 7 of them with comorbid CSU), followed by CholU ($n = 11$, 18.6%) and ColdU ($n = 4$, 6.8%, 3 of them with comorbid CSU), and three patients had two subforms of CIndU, one with SD and ColdU (patient was included in both disease groups) and two with SD and CholU (also included in both groups) (Tables S1 and S2). Baseline total IgE was measured in 27 patients before the first treatment of omalizumab. Autologous serum skin test (ASST) was performed in 24 patients by intradermal injection of autologous serum. Wheal formation to undiluted serum with a diameter that was at least 1.5 mm larger than that of the negative control, saline, 30 min after i.d. injection was considered as a positive ASST.⁶ The efficacy of omalizumab was evaluated by Urticaria Control Test (UCT) and Dermatology Life Quality Index (DLQI) at 1 month after each treatment. Patients were classified according to response: complete response (UCT = 16); well-controlled response (UCT ≥ 12); non-response (UCT < 12); fast response (UCT = 16 within the first 2 months); and no effect at all

on patient's life (DLQI = 1 or 0). Relapse was defined as the loss of CU control (UCT < 12) in complete responders after discontinuation of omalizumab.

All patients received 300 mg of omalizumab every month for up to 6 months. Fifty-nine patients were included at baseline and received the first treatment. Fifty-six, 47, 46, 45 and 36 patients received treatment at the end of the first through fifth month, respectively. Twenty-three patients were lost to follow-up (20 and 3 because they were unable to pay for treatment continuation or contracted COVID-19, respectively). Forty-six of 59 patients (78.0%) achieved well-controlled disease (UCT of 12 or more) during the course of their omalizumab treatment. Of these, 71.7% patients ($n = 33$; 55.9% of all patients) were complete responders (UCT = 16). Four of 5 (80.0%), 7 of 13 (53.8%) and 24 of 42 (57.1%) patients with ColdU, CholU and SD increased their UCT scores to 16, respectively. Of all ($n = 33$) complete responders at any time during their treatment, 60.6% ($n = 20$) responded within 2 months (fast responders), 15 of them (75.0%) within the first month. Two of 5 (40.0%), 4 of 13 (30.8%) and 16 of 42 (38.1%) patients with ColdU, CholU and SD were fast responders as assessed by UCT.

Chronic inducible urticaria patients treated with omalizumab experienced significant improvement of their QoL. Forty-nine (83.1%) showed a reduction of their DLQI score from baseline by more than 4, the minimal clinical importance difference (Figure S1). DLQI scores dropped to 1 or 0 (no QoL impairment) in 36 (59.3%) patients. All of 5 (100%), 7 of 13 (53.8%) and 26 of 42 (61.9%) patients with ColdU, CholU and SD achieved DLQI scores of 1 or 0, respectively. Of all ($n = 36$) patients who achieved complete normalization of their QoL (DLQI 1 or 0) at any time during their treatment, twenty-six (72.2%) did so within the first 2 months (fast responders) and sixteen of them (64.4%) within the first month. Two of 5 (40.0%), 5 of 13 (38.5%) and 21 of 42 (38.1%) patients with ColdU, CholU and SD were fast responders assessed with DLQI.

Patients with complete response to omalizumab ($n = 17$) were younger (30.9 ± 6.9 vs. 36.0 ± 11.5 years, $p = .039$), had a longer omalizumab treatment duration (median: 6.0 months vs. 3.5, $p < .001$) and higher baseline total IgE levels than those without (median: 98.0 vs. 42.9 kU/L, $p = .045$). All patients ($n = 5$) with

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TABLE 1 Predictors of complete response to omalizumab

	Response to omalizumab			p value
	Overall	UCT = 16	UCT < 16	
Female, n (%)	33 of 59 (55.9)	7 of 33 (21.2)	15 of 26 (57.7)	1.000
Disease duration, in months	21.0 (8.0, 37.0)	28.0 (6.5, 43.5)	18.0 (8.0, 34.5)	.327
UCT at baseline	4.0 (1.3, 8.0)	4 (3.0, 7.0)	6.0 (2.5, 9.0)	.419
DLQI at baseline	15.0 (8.0, 20.0)	18.0 (9.0, 20.0)	13.0 (4.0, 20.0)	.161
Treatment duration, in months	6.0 (5.0, 6.0)	6.0 (5.0, 6.0)	3.5 (3.0, 5.0)	.001
Comorbid CSU	10 of 59 (16.9)	6 of 33 (18.2)	4 of 26 (15.4)	1.000
Total IgE ^b , kU/L	79.0 (52.7, 231.0)	98.0 (68.1, 249.5)	42.9 (16.3, 223.5)	.045
IgE <40 kU/L ^b , n (%)	5 of 27 (18.5)	0 of 17 (0)	5 of 10 (50.0)	.003
Positive ASST ^c , n (%)	9 of 24 (37.5)	7 of 17 (41.2)	2 of 7 (28.6)	.669

Note: The total number of patients analysed was 59, and 33 (55.9%) had a UCT of 16, and 26 (44.1%) had a UCT of <16 in response to omalizumab treatment.

Bold = p value is <.05.

Abbreviations: ASST, autologous serum skin test; ClIndU, Chronic inducible urticaria; CSU, Chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; UCT, Urticaria Control Test.

^aPatients' age showed a normal distribution and is presented as mean ± standard deviation. The other continuous variables (UCT at baseline, DLQI at baseline, disease duration, total IgE) are presented as median with interquartile range. All categorized variables are compared by Fisher's Exact test.

^bIgE values from 27 patients were analysed.

^cASST responses from 24 patients were analysed.

baseline IgE <40 kU/L failed to achieve complete response to omalizumab ($p = .003$). There were no statistically significant differences between complete and incomplete responders with respect to gender, UCT scores at baseline, DLQI scores at baseline, disease duration, ASST results, comorbid CSU and subforms of CIndU (Table 1).

Patients with fast complete response ($n = 20$) had higher UCT scores (median: 4.2 vs. 2.5, $p = .031$) and lower DLQI scores at baseline (13.2 ± 6.1 vs. 17.8 ± 4.3 , $p = .022$) than those with slow complete response. Fast responders had numerically lower baseline total IgE levels than slow responders (median: 67.4 vs. 148.0 kU/L, $p = .058$), but this was not statistically significant. Gender, age, disease duration, ASST results, comorbid CSU and subforms of CIndU were not linked to the speed of achieving complete control with omalizumab treatment (Table 2).

Of 14 patients who achieved complete response within 6 months of omalizumab treatment, five stopped their treatment and all of them experienced relapse. One patient, with both ColdU and SD, experienced relapse of both of CIndUs at week 7 after treatment discontinuation. Two patients with SD relapsed in week 3 and week 6. The remaining two patients relapsed in week 9 (CholU) and week 14 (ColdU), respectively. All patients were successfully retreated with omalizumab and experienced complete response after the first administration. None of the patients reported adverse events resulting from their omalizumab treatment, and the treatment was generally well tolerated.

Our study found that omalizumab treatment, in patients with antihistamine refractory ColdU, CholU or SD, is associated with rapid and significant improvement of disease control and quality of life. Our study is the first to identify predictors of complete response and fast response to omalizumab treatment in CIndU patients and also one of the first to show that omalizumab treatment is linked to positive effects on life quality in CIndU patients.

The rate of well-controlled CIndU in our study is comparable to results from Spain (72.5%)⁴ and Canada (67.0%).⁵ Complete responders showed higher baseline total serum IgE in comparison with non-responders. All patients with low IgE (<40 kU/L) showed incomplete response. These findings suggest that IgE levels, in patients with CIndU, appear to be linked to treatment responses to omalizumab in a similar way that they are in CSU. They also suggest that, again similar to CSU, IgE contributes to the pathogenesis of CIndU in many but not all patients. CIndU patients who benefit from anti-IgE therapy may have IgE to autoantigens that result from being exposed to triggers of whealing and angioedema development. Exposure to these triggers, cold for example in patients with ColdU, would then lead to IgE-dependent skin mast cell degranulation in patients sensitized to the corresponding autoantigens (IgE-mediated autoimmunity/ autoallergy).⁷ While there is, as of yet, no direct evidence in support of this pathomechanism, it is supported by the results of passive transfer studies.⁷ In CIndU patients with low IgE levels, type IIb autoimmune mechanisms with mast cell-targeting and activating autoantibodies directed against

	Complete response after treatment (UCT = 16)		p value
	Fast response, within the first 2 months	Slow response, after the second month	
Age, in year ^a	32.6 ± 6.7	28.2 ± 6.5	.075
Female, n (%)	12 of 20 (60.0)	6 of 13 (46.2)	.493
Disease duration, in months	32.5 (8.8, 44.3)	13.0 (6.0, 43.0)	.786
UCT at baseline	4.5 (4.0, 7.8)	3.0 (1.5, 6.0)	.032
DLQI at baseline	13.2 ± 6.1	17.8 ± 4.3	.022
Comorbid CSU	3 of 20 (15.0)	4 of 13 (30.8)	.393
Total IgE ^b , kU/L	67.4 (58.9, 116.0)	148.0 (74.5, 272.5)	.058
IgE <40 kU/L ^b , n (%)	0 of 5 (0)	0 of 12 (0)	N/A
Positive ASST ^c , n (%)	4 of 7 (57.1)	3 of 10 (30.0)	.350

TABLE 2 Predictors of fast and slow response to omalizumab

Note: The total number of patients analysed was 33, and 20 (60.6%) showed a fast response within the first two month, and 13 (39.4%) showed a slow response after the second month.

Bold = p value is <.05.

Abbreviations: ASST, autologous serum skin test; CIndU, Chronic inducible urticaria; CSU, Chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; N/A, not applicable; UCT, Urticaria Control Test.

^aPatients' age and DLQI at baseline showed a normal distribution and is presented as mean ± standard deviation. The other continuous variables (UCT at baseline, disease duration, total IgE) are presented as median with interquartile range. All categorized variables are compared by Fisher's Exact test.

^bTotal IgE values from 17 patients were analysed here.

^cASST responses from 17 patients were analysed here.

IgE or its high affinity receptor may be relevant, but the evidence in support of this is scarce and of low quality. Type IIb autoimmune CSU comes with low IgE levels and slow and poor response to omalizumab treatment.⁸ As of now, there is only one study that describes anti-IgE autoantibodies and serum autoreactivity in patients with CIndU.⁹ Many questions regarding the pathogenesis of CIndU remain unanswered, and the characterization of the role and relevance of IgE has high priority.

Our study has several limitations including its retrospective approach, relatively low patient number and varying treatment duration across patients. Also, nearly 40 per cent of patients were lost to follow-up. The strengths of our study include the use of validated tools for assessing control and quality of life impairment in a real-life setting and its focus on the three most common forms of CIndU.

In conclusion, our study suggests that omalizumab is associated with rapid and significant improvement of disease control and quality of life in CIndU, especially in patients with high IgE. Slow responders have lower baseline UCT scores and higher baseline DLQI scores. These results, if confirmed by future studies, may help to guide patients' and physicians' expectations when omalizumab is used to treat CIndU.

CONFLICT OF INTEREST

Dr. Yu has nothing to disclose. Dr. Terhorst-Molawi has no disclosures. Dr. Altrichter reports grants and non-financial support from Allakos, grants and personal fees from AstraZeneca, grants from CSL Behring, non-financial support from Moxie, grants from Sanofi, outside the submitted work. Dr. Hawro has no disclosures. Dr. Chen has nothing to disclose. Dr. Liu has nothing to disclose. Dr. Song has nothing to disclose. Dr. Zhao reports grants from Novartis, outside the submitted work; Dr. Mauer reports grants and personal fees from Allakos, grants from Amgen, personal fees from Aralez, grants and personal fees from ArgenX, grants from AstraZeneca, personal fees from Celldex, grants and personal fees from CSL Behring, grants and personal fees from FAES, grants and personal fees from Genentech, grants and personal fees from GIINNOVATION, grants from Innate Pharma, grants from Kyowa Kirin, grants from Leo Pharma, grants from Lilly, grants and personal fees from Menarini, grants and personal fees from Moxie, grants and personal fees from Novartis, grants from Roche, grants and personal fees from Sanofi/Regeneron, grants and personal fees from UCB, grants and personal fees from Uriach, outside the submitted work.

AUTHOR CONTRIBUTIONS

Miao Yu substantial contributions to acquisition, analysis and interpretation of data; drafted the manuscript. Dorothea Terhorst-Molawi drafted the article. Sabine Altrichter drafted the article. Tomasz Hawro drafted the article. Yu-Di Chen substantial contributions to acquisition of data; drafted the article. Bo Liu participated in sample collection. Xiao-ting Song participated in sample collection. Zuo-tao Zhao substantial contributions to conception

and study design; reviewed the article critically for important intellectual content. Marcus Maurer substantial contributions to conception and study design; reviewed the article critically for important intellectual content. All authors were involved in final approval.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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