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[3,4]. Real life data on the efficacy and safety of omalizumab treatment in CIndU are limited[5-8].

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)[9] between February 2018 and May 2020. All 59 patients received 300 mg of omalizumab at least once and were refractory to H1-antihistamines at baseline **(Suppl.Table 1&2).** The efficacy of omalizumab was evaluated by Urticaria Control Test (UCT) and Dermatology Life Quality Index (DLQI) at one 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); no effect at all on patient's life (DLQI=1 or 0).

Complete, well-controlled, fast response was achieved in 33 (55.9%), 46 (78.0%), 20 (60.6% of complete responders) patients. Four of 5 (80.0%), 7 of 13 (53.8%) and 24 of 42 (57.1%) patients with cold urticaria (ColdU), cholinergic urticaria (CholU), and symptomatic dermographism (SD) increased their UCT scores to 16. Complete normalization of quality of life (QoL) was achieved in 36 (61.0%) patients, and 26 of them (72.2%) were fast responders. All of 5 (100%), 7 of 13 (53.8%), and 26 of 42 (61.9%) patients with ColdU, CholU, and SD achieved DLQI = 1 or 0. Of 59 patients, 49 (83.1%) showed a reduction of their DLQI score by more than 4, the minimal clinical importance difference **(Suppl.Fig. 1).** None of the patients reported

adverse events resulting from their omalizumab treatment, and the treatment was generally well tolerated.

Patients with UCT=16 were younger (30.9 ± 6.9 vs. 36.0 ± 11.5 years, *P*=0.039), had a longer treatment duration (median: 5.0 months vs. 1.0, *P*=0.033), and higher baseline total IgE levels than those without (median: 98.0 vs. 42.9 kU/L, *P*=0.045). Patients (n=5) with baseline IgE <40kU/L failed to achieve complete response (*P*=0.003) **(Table 1).** Fast responders had higher UCT scores (median: 4.2 vs. 2.5, *P* =0.031) and lower DLQI scores at baseline (13.2 ± 6.1 vs. 17.8 ± 4.3, *P* =0.022) **(Table 2)**.

Our study confirms that omalizumab, in patients with antihistamine refractory ColdU, CholU, or SD, provides 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 significantly improves QoL of CIndU patients.

The rate of well-controlled CIndU in our study is comparable to results from Spain (72.5%)[5] and Canada (67.0%)[6]. Complete responders showed higher baseline total serum IgE in comparison with non-responders. All patients with low IgE showed incomplete response. These findings suggest that IgE plays a role in the pathogenesis of CIndU in most but not all patients.

Our study has several limitations including its retrospective approach, relatively low patient number, and varying treatment duration across patients. Its strengths 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 can be an effective therapy 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.

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Conflict of Interest:

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Table 1 Predictors of complete response to omalizumab

	Overall	Response to omalizumab		*P*
		UCT =16 (n=33, 55.9%)	UCT < 16 (n=26, 44.1%)	
Age (in years) †	33.1 ± 9.5	30.9 ± 6.9	36.0 ± 11.5	**0.039***
Female, n (%)	33 (55.9)	7 (58.3)	15 (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)	0.327
UCT at baseline	4.0 (1.3, 8.0)	4 (3, 7)	6.0 (2.5, 9.0)	0.419
DLQI at baseline†	15.0 (8.0, 20.0)	18.0 (9.0, 20.0)	13.0 (4.0, 20.0)	0.161
Omalizumab treatment duration, in months	2.0 (1.0, 6.0)	5.0 (1.5, 6.0)	1.0 (1.0, 5.0)	**0.033***
Comorbid CSU				
Yes, n (%)	10 (18.6)	6 (60.0)	4 (40.0)	1.000
No, n (%)	49 (81.4)	27 (55.1)	22 (44.9)	
Total IgE, kU/L (n=27)	79.0 (52.7, 231.0)	98.0 (68.1, 249.5)	42.9 (16.3, 223.5)	**0.045***
IgE ≥ 40 kU/L, n (%)	22 (81.5)	17 (77.3)	5 (22.7)	**0.003***
IgE < 40 kU/L, n (%)	5 (18.5)	0	5 (100)	
ASST (n=24)				
Positive, n (%)	9 (37.5)	7 (77.8)	2 (22.2)	0.669
Negative, n (%)	15 (62.5)	10 (66.7)	5 (33.3)	

†The age and DLQI at baseline are normal distribution and are 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. *A *P* value is less than 0.05. Abbreviations: CIndU, Chronic inducible urticaria; CSU, Chronic spontaneous urticaria; UCT, Urticaria Control Test; DLQI, Dermatology Life Quality Index; ASST, autologous serum skin test; ColdU, cold urticaria; CholU, cholinergic urticaria; SD, Symptomatic dermographism.

Table 2 Predictors of fast and slow response to omalizumab

	Complete response after treatment (UCT =16)		
	Fast response (n ≤ 2 months) (n=20, 60.6%)	**slow response (n ≥ 3 months) (n=13, 39.4%)**	***P***
Age (in years) †	32.6±6.7	28.2±6.5	0.075
Female, n (%)	12 (66.7)	6 (33.3)	0.493
Disease duration, in months	32.5 (8.8, 44.3)	13.0 (6.0, 43.0)	0.786
UCT at baseline	4.5 (4.0,7.8)	3.0 (1.5, 6.0)	**0.032***
DLQI at baseline	13.2±6.1	17.8±4.3	**0.022***
Comorbid CSU			
Yes, n (%)	3 (42.9)	4 (57.1)	0.393
No, n (%)	17 (65.4)	9 (34.6)	
Total IgE, kU/L (n=18)	67.4 (58.9, 116.0)	148.0 (74.5, 272.5)	0.058
IgE ≥ 100 kU/L, n (%)	1 (12.5)	7 (87.5)	0.294
IgE < 100 kU/L, n (%)	4 (44.4)	5 (55.6)	
ASST (n= 17)			
Positive, n (%)	4 (57.1)	3 (42.9)	0.350
Negative, n (%)	3 (30.0)	7 (70.0)	

†The age and DLQI at baseline are normal distribution and are 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. *A P value is less than 0.05. Abbreviations: CIndU, Chronic inducible urticaria; CSU, Chronic spontaneous urticaria; UCT, Urticaria Control Test; DLQI, Dermatology Life Quality Index; ASST, autologous serum skin test; ColdU, cold urticaria; CholU, cholinergic urticaria; SD, Symptomatic dermographism.