

Report

Treatment response to omalizumab in patients with refractory chronic spontaneous urticaria

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Abstract

Background Previous clinical trials have demonstrated the efficacy and safety of the anti-IgE monoclonal antibody omalizumab in chronic spontaneous urticaria (CSU) not responding to antihistamine treatment. The primary aim of our study was to describe the response patterns of patients with refractory CSU treated with omalizumab in a real-world clinical setting.

Methods A retrospective analysis of medical records of 20 patients with refractory CSU was performed. Demographic, clinical, and laboratory features were retrieved and analyzed in correlation with treatment data.

Results Mean age of our patient population was 54.5 years, while the majority were females (15/20 cases, 75%). Mean disease duration prior to omalizumab administration was 21.8 months. All patients had a history of chronic urticaria, refractory to high antihistamine and corticosteroid treatment, and responded favorably to omalizumab after administration of 1–5 doses of omalizumab; complete response was observed in 17/20 patients (85%) and well-controlled disease in the remaining 3/20 patients (15%). In a subset of cases (6/20, 30%), best response to omalizumab was achieved after interval administration of a 9-day course of methylprednisolone (total dose of 188 mg). Late response to omalizumab (after three-month treatment) was significantly correlated ($P = 0.026$) with shorter disease duration before initiation of omalizumab.

Conclusion In the present series, omalizumab, either alone or in combination with a short-term course of corticosteroids, was highly effective in resolution of refractory CSU. Furthermore, disease duration prior to omalizumab had a significant effect on timing of response.

Introduction

Chronic spontaneous urticaria (CSU), which has generally replaced the former term chronic idiopathic urticaria (CIU), is defined by the presence of pruritic wheals (hives), angioedema, or both, that persist or recur for a period of at least 6 weeks and do not seem to be induced by any apparent external stimuli.^{1,2} The severity and duration of CSU may vary greatly among patients, while its impact on quality of life can be significant, especially in the presence of concurrent angioedema and when symptoms last for several years or fail to adequately respond to standard therapeutic interventions.^{3–6}

According to the latest international guidelines, daily administration of nonsedating, second-generation, H1-antihistamines is the "gold-standard" first-line treatment of CSU, while dose-escalation (up to fourfold the licensed daily dose) of H1-antihistamines is typically followed as a second-line approach when symptoms persist for more than 2 weeks after the initial

treatment course.^{1,2,7} The use of sedating, first-generation antihistamines for CSU treatment has been largely abandoned, particularly in Europe.^{1,7} Administration of these drugs (at bedtime only) is nevertheless included, as an alternative to dose advancement of H1-antihistamines, in the US guidelines, while addition of another second-generation antihistamine or an H2-antagonist are among the second-line treatment options recommended by both British and US associations.^{2,7} A subset of patients, comprising approximately one-third of all cases, may nevertheless remain symptomatic despite use of the above therapeutic measures, suggesting the suboptimal effectiveness of antihistamines in CSU.⁸

Previous clinical trials – including the pivotal ASTERIA I and II and GLACIAL studies^{9–11} – and a recent meta-analysis of clinical trial data¹² have all supported that the humanized anti-IgE monoclonal antibody omalizumab may represent a safe and effective third- or fourth-line treatment option in cases with CSU refractory to standard antihistamine treatment. Real-world data

on the safety and efficacy of omalizumab in this patient population are nevertheless limited, while other clinically significant aspects, such as prediction of the timing of response to omalizumab, remain essentially unexplored.

The primary objective of our study was to further describe the response patterns to omalizumab in a real-world population of patients with refractory CSU, based on the experience of our department. The secondary objective was to identify potential clinical and laboratory predictors of response and timing of response to omalizumab treatment.

Materials and methods

Patient population and study design

This study is a retrospective case series of patients with refractory CSU, diagnosed and treated in the Allergy Department of Sotiria Athens General Hospital, between January 2014 and December 2016. Diagnosis of CSU was made by an experienced allergist/immunologist and was based on previously published guidelines. Patient inclusion criteria were predefined as follows: clinician-confirmed diagnosis of CSU; persistence or recurrence of symptoms for at least 4 weeks after up dosing (fourfold the licensed dose) of second-generation nonsedating H1-antihistamines and administration of repeated courses of oral corticosteroids; omalizumab administration. Patients with inducible urticarias or those who had not received oral corticosteroids for symptomatic control were excluded.

The medical records of all identified cases were reviewed; extracted data included age at diagnosis, gender, disease duration (from onset of symptoms to omalizumab administration), presence of angioedema, history of clinically relevant comorbidities, laboratory testing results, including total immunoglobulin E (IgE) levels, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and thyroid stimulation hormone (TSH) levels, antinuclear (ANA) and antithyroid antibodies status, autologous skin serum test (ASST) results, and treatment data (treatment response to omalizumab, number of omalizumab doses at the time point of best response, total number of omalizumab doses administered, corticosteroids administration and follow-up time). All laboratory values were measured using standardized laboratory procedures. ASST was performed according to the technique previously described by Sabroe *et al.*¹³

Assessment of CSU activity and definitions of response

Weekly Urticaria Activity Score (UAS7) was used for the assessment of urticaria severity (prior to omalizumab administration), with scores ranging from 0 (no pruritus, no hives for a period longer than 7 days) to 28–42 (severe CSU with marked pruritus and more than 50 hives/day or large confluent areas of hives), while intermediate values (1–6, 7–15, and 16–27) were classified as well-controlled, mild, and

moderate CSU, respectively, as previously described.^{8,14} Post-treatment values of UAS7 were also used for the evaluation of treatment response; patients with $UAS7 \leq 6$ were classified with well-controlled disease, while those with $UAS7 = 0$ as complete responders, according to previous recommendations.^{8,14} Patients with complete control or well-controlled disease were classified as responders. Treatment response was classified as early when noted within the first month of treatment and late when noted after a time period of 3 months, as previously proposed.¹⁵ Responses noted within the remaining timeframe - second to third month of treatment - were classified as intermediate. The timing of treatment response (early/intermediate versus late) was correlated with the demographic, clinical, and laboratory parameters of patients.

Statistical analysis

Continuous variables are presented with mean and standard deviation (SD). Quantitative variables are presented with absolute and relative frequencies. Fisher's exact tests were used for the comparison of categorical variables between those with early/intermediate and those with late treatment response. Student's *t*-tests were computed for the comparison of continuous data between the two aforementioned groups of patients. All *P* values reported are two-tailed. Statistical significance was set at 0.05, and analyses were conducted using SPSS statistical software (version 19.0).

Results

Demographic, clinical, and laboratory data

The study population comprised 20 patients with refractory CSU, among a total of 94 cases of CSU diagnosed and treated in our department during the same time period (January 2014 to December 2016). The demographic, clinical, and laboratory data of all studied cases are summarized in Table 1. Mean age of our patient population was 54.5 years (range 19–85 years), while the majority were females (15/20 cases, 75%). Angioedema was present in 10/20 cases (50%). Mean disease duration prior to omalizumab administration was 21.8 months (range 3–60 months). A history of Hashimoto's thyroiditis was recorded in five cases and diabetes in two cases, while one patient each had a history of hypothyroidism, hyperthyroidism, pemphigus vulgaris, gastroesophageal reflux disease (GERD), hypertension, or coronary artery disease, respectively.

ASST was performed in 15/20 patients (75%), with positive results in 9/15 cases (60%). Serum levels of total IgE, ESR, CRP, and TSH were elevated in 3/20 (15%), 14/20 (70%), 10/20 (50%), and 0/12 cases (0.0%), respectively; TSH levels were decreased in two patients (2/20, 10%). Positive ANA and antithyroid antibodies were found in 8/20 (40%) and 6/20 cases (30%), respectively.

Table 1 Demographics, clinical data, and laboratory test results

Case (N)	Age	Gender	Significant comorbidities	Presence of angioedema	Disease duration pre-omalizumab (months)	Laboratory test results					
						ESR	CRP	IgE	TSH	Autoimmunity	ASST
1	60	Female	Hashimoto's thyroiditis	No	35			WNL	WNL	Antithyroid Antibodies + ANA +	Positive
2	68	Female	None	Yes	15			WNL	WNL	No	Positive
3	85	Male	None	No	7			WNL	WNL	No	Positive
4	71	Female	None	No	7		WNL	WNL	WNL	No	Positive
5	56	Female	None	Yes	8				WNL	No	Negative
6	53	Male	None	No	53	WNL	WNL	WNL	WNL	No	Not performed
7	84	Male	None	No	22		WNL		WNL	No	Not performed
8	75	Female	Hashimoto's thyroiditis	Yes	3			WNL	WNL	Antithyroid Antibodies + ANA +	Not performed
9	67	Female	None	No	29		WNL	WNL	WNL	No	Not performed
10	56	Female	Pemphix	Yes	3			WNL	WNL	ANA+	Not performed
11	25	Female	Hashimoto's Thyroiditis	Yes	11			WNL	WNL	Antithyroid Antibodies +	Positive
12	30	Female	None	Yes	5	WNL	WNL	WNL	WNL	ANA+	Negative
13	54	Female	Hypothyroidism GERD	No	49	WNL	WNL	WNL	WNL	No	Negative
14	52	Female	Hashimoto's thyroiditis	No	2	WNL		WNL	WNL	Antithyroid Antibodies +	Negative
15	29	Female	Hashimoto's thyroiditis	Yes	5		WNL	WNL	WNL	Antithyroid Antibodies + ANA +	Positive
16	24	Male	None	Yes	48	WNL	WNL		WNL	ANA +	Negative
17	52	Female	None	Yes	20	WNL	WNL	WNL	WNL	No	Positive
18	19	Female	Hyperthyroidism	No	40		WNL	WNL		Antithyroid Antibodies + ANA +	Positive
19	65	Female	Diabetes Hypertension	No	60			WNL		ANA +	Positive
20	66	Male	Diabetes Coronary Heart Disease	Yes	15			WNL	WNL	No	Negative

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; GERD, gastroesophageal reflux disease; IgE, total immunoglobulin E; TSH, thyroid-stimulating hormone; ASST, autologous skin serum test; ANA, antinuclear antibodies; WNL, within normal limits.

Treatment response

Treatment data are presented in Table 2. Prior to omalizumab administration, all patients had refractory CSU with persistent or recurrent symptoms despite use of high-dose H1-antihistamines and repeated courses of oral corticosteroids. Pre-omalizumab UAS7 ranged from 11 to 42 (mean: 34). Post-omalizumab UAS7, corresponding to the best response to omalizumab, was zero (complete response) in 17/20 patients (85%), and six or four (well-controlled disease) in the remaining 3/20 patients (15%), after administration of one to five doses of omalizumab (mean: 2.7). Overall, response to omalizumab after the first omalizumab dose ("early" response) was noted in almost half our studied cases (9/20 cases, 45%), after the second dose ("intermediate" response) in 2/20 cases (10%), while the remaining patients responded after the fourth or fifth dose ("late"

response) (9/20 cases, 45%). Among all responders (20/20 patients, 100%), a direct response to omalizumab was observed in 14/20 cases (70%), following the first or second omalizumab dose in nine and two patients, respectively, and the fourth omalizumab dose in 3 patients. In the remaining cases (6/20, 30%), the best response to omalizumab was achieved only after interval administration of a single 9-day course of methylprednisolone (total dose of 188 mg) (Table 3). Best response in these refractory cases was observed after administration of five or four doses of omalizumab in four and two cases, respectively. The total number of omalizumab doses administered in all patients ranged from 3 to 17 (mean: 10.8). Mean follow-up time in all cases was 16.6 months (range: 3–26 months). At the last follow-up, treatment was ongoing in 10/20 cases (50%). No severe adverse events were recorded during omalizumab

Table 2 Treatment and follow-up data of our patient population

Case (N)	Pre-OMB UAS7	Post-OMB UAS7 (best response)	Treatment response	Timepoint of best response to OMB (number of OMB doses)	Total number of OMB doses	Follow-up time
1	42	0	Complete response*	5	11	24 months
2	42	0	Complete response*	4	10	26 months
3	42	0	Complete response*	5	11	15 months
4	35	6	Well-controlled urticaria	1	16	16 months
						Ongoing treatment
5	42	0	Complete response	1	7	14 months
6	35	0	Complete response	1	7	20 months
7	40	0	Complete response	1	7	25 months
8	42	0	Complete response*	5	11	22 months
9	35	0	Complete response	1	7	17 months
10	42	0	Complete response	4	10	16 months
11	28	0	Complete response	1	7	22 months
12	42	6	Well-controlled urticaria*	4	5	5 months
						Ongoing treatment
13	24	0	Complete response	1	17	17 months
						Ongoing treatment
14	23	0	Complete response	4	16	16 months
						Ongoing treatment
15	42	0	Complete response	1	11	11 months
						Ongoing treatment
16	25	0	Complete response	1	17	17 months
						Ongoing treatment
17	32	0	Complete response*	5	15	15 months
						Ongoing treatment
18	28	0	Complete response	2	3	3 months
						Ongoing treatment
19	11	4	Well-controlled urticaria	2	17	17 months
						Ongoing treatment
20	28	0	Complete response	4	11	13 months

OMB, omalizumab.

*Response was achieved after interval administration of a 9-day course of corticosteroids.

administration. There were no rebound symptoms in any of our patients and only one case (case 4; 1/12, 8.3%) of recurrence after discontinuation of omalizumab treatment.

As shown in Table 4, disease duration was significantly lower in patients with late response as compared to those with early response ($P = 0.026$). The remaining clinical, demographic, and laboratory data were not found to be significantly associated with timing of response to omalizumab ($P > 0.05$ in all cases).

Discussion

In the present cohort of patients with chronic refractory CSU, omalizumab treatment was highly effective in achieving disease control in all cases, with complete control in the overwhelming majority of them. Best response to omalizumab was observed after administration of the first omalizumab dose in 50% of our studied cases, while delayed responses (after four of five doses of omalizumab) were noted in the remaining patients. These findings are well within the range of those reported by previous

investigators, suggesting that a significant percentage of patients may respond to omalizumab within the first month of treatment.^{9–11,16,17} In the ASTERIA I, ASTERIA II, and GLACIAL clinical trials,^{9–11} CSU was well-controlled after a single dose of omalizumab 300 mg in 37%, 51%, and 37% of patients, respectively, while in another two-center prospective case series by Sussman *et al.*,¹⁶ 44.1% of patients achieved complete remission of CSU symptoms after the first dose of omalizumab 150 mg.

As further documented in the above studies, response to omalizumab may be dose-dependent, increasing with administration of higher doses (300 mg vs. 150 and 75 mg), while continuous dosing of omalizumab may also increase the percentage of responders.^{9–11,16} Patients requiring more than 3-monthly doses to respond have been described as late responders, and it has been emphasized that discontinuation of omalizumab treatment before administration of a minimum of three doses is contraindicated, as it may lead to suboptimal response rates.¹⁵ The exact mechanism underlying these late responses remains,

Table 3 Corticosteroids (oral methylprednisolone/16 mg) administration protocol

Day	Dosage	Total dosage (cumulative)
1	32 mg twice daily	64 mg
2	32 mg once daily 16 mg once daily	112 mg
3	32 mg once daily	144 mg
4	16 mg once daily	160 mg
5	12 mg once daily	172 mg
6	8 mg once daily	180 mg
7	4 mg once daily	184 mg
8	–	184 mg
9	4 mg once daily	188 mg

Table 4 Association of demographic, clinical, and laboratory parameters of patients according to the timing of response to omalizumab

Patient parameters	Response to omalizumab		P*
	Early/Intermediate N (%)	Late N (%)	
Age (years), mean (SD)	49.7 (22.1)	60.4 (15.8)	0.278
Gender			
Female	8 (72.7)	7 (77.8)	>0.999
Male	3 (27.3)	2 (22.2)	
Comorbidities			
No	6 (54.5)	4 (44.4)	>0.999
Yes	5 (45.5)	5 (55.6)	
Angioedema			
No	7 (63.6)	3 (33.3)	0.370
Yes	4 (36.4)	6 (66.7)	
Disease duration (months), mean (SD)	30.2 (20.6)	11.7 (10.9)	0.026
ESR			
Normal	3 (27.3)	3 (33.3)	>0.999
Elevated	8 (72.7)	6 (66.7)	
CRP			
Normal	8 (72.7)	2 (22.2)	0.070
Elevated	3 (27.3)	7 (77.8)	
IgE			
Normal	8 (72.7)	9 (100)	0.218
Elevated	3 (27.3)	0 (0)	
TSH			
Normal	9 (81.8)	9 (100)	0.479
Decreased	2 (18.2)	0 (0)	
Autoimmunity			
No	6 (54.5)	4 (44.4)	>0.999
Yes	5 (45.5)	5 (55.6)	
Pre omalizumab UAS7, mean (SD)	31.4 (9.3)	37.2 (7.5)	0.146

*Statistically significant values are marked with bold.

nevertheless, unclear, while it also remains unknown whether clinical or laboratory parameters of patients may predict timing of response to omalizumab. In our cohort, late response to

omalizumab was correlated with shorter disease duration before initiation of omalizumab. We can only hypothesize that this potential correlation may be due to the presence of more active disease among patients with more recent onset of symptoms. Evidently, given the lack of previous data, our small patient sample and the limitations pertaining to our study design (retrospective case series), these highly preliminary findings warrant confirmation in larger prospective series.

According to previously published guidelines for the treatment of CSU, a short-term course of corticosteroids (up to 10 days) may be used when clinically needed for symptom control at any treatment stage and particularly for severe disease exacerbations.^{1–3,7} Although patients almost invariably respond to corticosteroids, protracted use of steroids is not advised due to the well-known adverse side effect profile – such as hypertension, osteoporosis, and rebound of symptoms upon withdrawal – associated with their administration on a chronic basis.¹⁸ An interesting clinical observation derived from our case series is that a subset of patients who had initially failed to respond to omalizumab achieved immediate and sustained responses after a 9-day course of methylprednisolone, administered in-between omalizumab injections, without discontinuation or alteration of the initial omalizumab treatment protocol. Given the fact that these patients had received repeated courses of corticosteroids prior to omalizumab treatment with only temporary control of symptoms, it is conceivable that the ultimate treatment effect observed may have resulted from a combined effect of omalizumab and corticosteroids. Similar to our findings, a previous research group reported successful use of short-term systemic glucocorticoid therapy as a bridging intervention until administration of the next injection of omalizumab in real-world patients with severe CSU.¹⁶ The potential synergy between steroids and omalizumab might be an issue deserving further investigation.

In conclusion, the results of our single-institution case series attest to the real-world safety and efficacy of omalizumab in severe refractory CSU. A subset of our patient population, who had initially failed to show an early response to omalizumab, showed sustained response to the drug after administration of a short-term interval of corticosteroids. Furthermore, shorter disease duration was correlated with late response to omalizumab. Additional prospective cohorts of patients with severe refractory CSU are warranted to confirm these findings and identify potential independent predictors of response and timing of response to omalizumab.

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