ORIGINAL ARTICLE

Omalizumab as monotherapy for refractory chronic idiopathic urticaria: A prospective noncomparative open study from Kuwait

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ABSTRACT

Background: Omalizumab, a recombinant humanized IgG1κ anti-IgE antibody that reduces levels of free serum IgE. Few case reports have shown beneficial effects of omalizumab in patients with recalcitrant or therapy resistant chronic idiopathic urticaria (CIU).

Objective: To evaluate the efficacy of omalizumab as monotherapy in patients with moderate to severe refractory CIU, not responding satisfactorily to any other therapeutic modality.

Patients and methods: Twelve patients diagnosed with moderate to severe CIU, with persistent symptoms for at least 6 weeks despite several treatment modalities, were treated with placebo for 4 weeks followed by omalizumab (300mg) every 2 or 4 weeks for 16 weeks. Primary efficacy variable was change from baseline to the final 4 weeks of omalizumab treatment in mean Urticaria Activity Score (UAS, 0-9 scale). Changes in rescue medication used and safety as well as tolerability of the drug were also assessed.

Results: Mean UAS declined from 6.68±1.33 to 0.55±0.59 with $P < 0.001$ from baseline to the final 4-week period of omalizumab treatment. Complete absence of wheal development, erythema, pruritus and interference with daily activity was observed in 91.67 %, 75%, 66.67% and 75% patients, respectively and the use of rescue medication reduced significantly ($P< 0.05$) from 3.87±0.56 tablets at baseline to 0.48±0.36 tablets during the final 4-week period of omalizumab treatment. Seven patients were completely symptom free and adverse side effects were recorded in four patients. No new safety concerns regarding laboratory parameters or clinically relevant vital signs were observed.

Conclusion: Omalizumab in an effective immunosuppressive sparing new treatment modality for moderate to severe refractory CIU patients with good overall safety and tolerability profile.

KEYWORDS: Chronic idiopathic urticaria, autoantibody, omalizumab, anti-IgE, urticaria activity score

INTRODUCTION

Chronic idiopathic urticaria (CIU) is defined as spontaneous emergence of wheals, angioedema, or both without any specific cause in the United States or chronic spontaneous urticaria in Europe if symptoms occur daily or almost daily for more than 6 weeks.[1] It affect 1% to 3% of people in western countries.[2] CIU has a significant effect on patient's quality of life affecting both physical and psychological aspects similar to that experienced by sufferers from triple-vessel coronary artery disease.[3,4]

CIU symptoms are brought about by degranulation of skin mast cells. In approximately half of the patients with CIU, no cause for the condition has been identified.[5,6] 35-45% of patients possess autoimmune IgG antibodies that target the alpha subunit of FcεRI or, to a lesser extent, target directly the IgE antibody.[6,7] A link between thyroid autoimmunity and chronic urticaria has also been observed in a subset of patients.[8]

H1-antihistamines are the mainstay of symp-

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tomatic therapy. However, less than half of patients with CIU achieve sufficient symptom control with antihistamines at standard doses.[9] Current guidelines for the treatment of CIU recommend a stepwise approach beginning with nonsedating H1-antihistamines (nsAHs) and then increasing the dose of nsAH up to 4-fold if symptoms persist before changing to a different nsAH or adding a leukotriene antagonist. If symptoms do not abate with any of these interventions, the guidelines recommend adding cyclosporin A, an H2-antihistamine, dapsone, or omalizumab.[9] Cyclosporine has been shown to be effective when administered with an nsAH,[10] but concerns about potential toxicities preclude it from being recommended as standard treatment.[9] Data on the combination of H1- and H2-antihistimines is favorable but limited, and dapsone has only been tested in uncontrolled clinical trials.[9] Exacerbations are treated with systemic steroids for 3 to 7 days, but long term exposure is not recommended because of unavoidable severe adverse events (AEs).[9]

Omalizumab is a recombinant humanized IgG1κ anti-IgE antibody that selectively binds to the C3 domain of the IgE heavy chain (ie, the site where IgE would bind to FceRI) and thereby reduces levels of free IgE in serum.[11] In addition, because occupancy of FceRI by IgE determines the levels of surface FceRI expression, reduced binding of IgE to FceRI leads to a downregulation of FceRI expression on mast cells and basophils.[12,13] Additionally, omalizumab has been shown to produce immune-modulating effects beyond IgE and its receptors, including effects on peripheral eosinophil and T-lymphocyte function.[14,15] Omalizumab dosage may range according to different authors between 0.016-0.50 mg/kg at dosage interval of 2-4 weeks.[16] The drug is administered subcutaneously and reaches peak serum levels 7-8 days after drug administration. A decrease of free serum levels of IgE of more than 96% is achieved within 1 hour after the first dose and is maintained between doses.[17]

Initially omalizumab use was restricted mainly to severe asthmatics. However, recent reports suggest that omalizumab may play role in the treatment of other allergic disorders as well as in immunotherapy.[16] After initial case reports of beneficial effects of omalizumab in patients with chronic urticaria,[18,19] three proof-of-concept trials investigated omalizumab in patients with active CIU who remained symptomatic despite antihistamine therapy.[20,21,22] Lately case reports of beneficial effects of omalizumab in patients with recalcitrant or therapy resistant CIU have been published.[23,24,25] Therefore the present study was conducted to assess the efficacy of omalizumab as monotherapy in patients with CIU who were refractory to all kinds of therapy but showed good response to omalizumab as measured by urticaria activity score (UAS). In addition, the safety and tolerability of omalizumab were also assessed.

PATIENTS AND METHODS

Male and female patients aged 18 to 70 years with a clinical diagnosis of moderate-to-severe refractory CIU (as classified by the latest consensus guidelines from the European Academy of Allergology and Clinical Immunology -EAACI) with persistent symptoms for >6 weeks despite receiving maximal antihistamine therapy (H1 antihistamines up to four times daily), leukotriene antagonist, H2 antihistamines,

systemic steroids, dapsone and immunoglobulins, at screening were eligible for enrollment in the study. Patients were excluded from the study if they had acute urticaria, urticarial vasculitis, chronic diarrhea, pregnant or lactating mothers, renal dysfunction, history of epilepsy, malignancy within the past 5 years, cerebrovascular attacks or ischemia. At the screening visit, complete history, physical examination and laboratory evaluations including complete blood count, erythrocyte sedimentation rate, liver function test, kidney function test, thyroid function test, antithyroglobulin antibody, antimicrosomal antibody, total IgE as well as stool evaluation for parasites, electrocardiogram and clinical assessment of urticaria and angioedema was done. A 1-week screening period was used to establish further patient eligibility. All patients maintained a daily diary to record urticaria signs and symptoms based on a scoring system (0-3) as shown in Table 1. Pruritus severity had to be at least mild (score of 1on a 0-3 scale), and the Urticaria Activity Score (UAS), a combination of pruritus severity, number of hives, and size of largest hive, had to be at least moderate (minimum score of 4 on a 0-9 scale).

After inclusion criteria were met, patients were steadily weaned off all other medications, except for the antihistamine, 4 weeks before the start of omalizumab. All patients received placebo for 4 weeks and then omalizumab for 16 weeks. Patients were blind to treatment sequence. Omalizumab was administered consistent with the US product label every 2 weeks or every 4 weeks, dosed according to the patient's body weight, and serum IgE obtained at the screening visit. The maximum treatment study period was 4 months. Patients were permitted to take 25 to 50 mg hydroxyzine as often as 4 times a day as needed throughout the study. The use of hydroxyzine was tabulated at each study visit. Daily diaries for urticaria signs and symptoms were maintained throughout the study. The response to treatment was assessed at monthly visits based on the severity of clinical signs during each visit. Accordingly, the mean UAS was calculated. Patients were followed up for 6 month after they had finished omalizumab to monitor any relapse of signs or symptoms and to collected safety data.

The primary efficacy variable was the change from baseline in mean UAS (ie, the average over the 4-week placebo treatment period) to the final 4-week period of omalizumab treatment. Secondary efficacy variables included the change from baseline in interference with daily activities, pruritus severity score, erythema severity score, no. of wheels score and rescue medication used. A P value of <0.05 was considered significant. The protocol of the study was approved by the institutional ethics committee of our hospital and informed consent was

Table 1 Urticaria activity scoring (UAS) system

Score	Number of wheals	Pruritus severity	Erythema severity	Interference with daily activities
0	None	None	None	None
1	Less than 20	Mild, minimal alertness, easily tolerated	Slight	Mild, not upsetting, little effect on activity
2	20–50 wheals	Moderate, distinct alertness, annoying but tolerable	Moderate	Moderate, some interference with activity
3	>50 wheals	Severe, hard to tolerate	Significant	Severe, daily activities significantly or completely reduced

obtained in writing from all the patients before starting the treatment.

RESULTS

We treated 12 patients with moderate to severe refractory Chronic Idiopathic Urticaria (CIU) with omalizumab, at the Department of Dermatology, Farwaniya hospital, Kuwait over a period of 2 years (July 2009 to July 2011). The majority of patients in this study were males (58.33%) with male to female ratio of 7:5. The age ranged between 23 to 68 years, with the mean age being 40.16±12.97 years. Study subjects had CIU for periods ranging from 2 years to 33 years, with mean duration of 12.92 years. None of the patient's had satisfactory response to maximal dose antihistamine therapy and other adjuvant therapeutics used. Patient Demographics and Clinical Characteristic are summarized in Table 2.

There was significant improvement in all the patients, with reduction from severe and therapy-resistant urticaria before omalizumab treatment to urticaria that is controlled by omalizumab alone or with on-demand antihistamines. Four patients received omalizumab twice monthly

Table 2 Demographic and clinical characteristics of the nine CIU patients

Pt. No.	Urticaria and relevant history	Age	Sex	Duration of CIU (years)	Previous medication	Total IgE (kU/l)	Dose of omalizumab
1	Chronic idiopathic urticaria, cholinergic urticaria, Dermographism	52	*m	16	H1 AH# up to four times, long-term steroids,	2157	300 mg, twice monthly
2	Chronic idiopathic urticaria, , atopic dermatitis	25	m	14	H1 AH up to four times, and more, steroids, immunoglobulins	258	300 mg, monthly
3	Chronic idiopathic urticaria, increased thyroid antibodies,	49	**f	22	H1 AH up to fourfold, steroids	3081	300 mg, twice monthly
4	Chronic idiopathic urticaria, chronic sinusitis	27	f	5	H1 AH up to four times, leukotriene antagonist, dapsone, steroids	759	300 mg, monthly
5	Chronic idiopathic urticaria, , angioedema	39	m	4	H1 AH, up to four times, H2-antihistamines leukotriene antagonist, steroids	1920	300 mg, twice monthly
6	Chronic idiopathic urticaria, asthma	42	f	2	H1 AH up to four times,, leukotriene antagonist, steroids	514	300 mg, monthly
7	Chronic idiopathic urticaria, angioedema, hypertension, asthma,	41	m	6	H1 AH up to four times, leukotriene antagonist, H2- antihistamines, steroids	1145	300 mg, twice monthly
8	Chronic idiopathic urticaria, , atopic dermatitis	31	f	14	H1 AH up to four times, leukotriene antagonist	219	300 mg, monthly
9	Chronic idiopathic urticaria, hypothyroidism, cholinergic urticaria	37	m	14	H1 AH up to four times, leukotriene antagonist, long term steroids	367	300 mg, monthly
10	Chronic idiopathic urticaria, asthma	68	f	33	H1 AH up to four times, montelukast	212	300 mg, monthly
11	Chronic idiopathic urticaria, chronic sinusitis, atopic dermatitis	48	m	17	H1 AH up to four times, steroids	98	300 mg, monthly
12	Chronic idiopathic urticaria, multiple allergies, flush	23	m	8	H1 AH up to four times, long term steroids	714	300 mg, monthly

#H1 AH- H1-antihistamines

*m = male

**f = female

because of their IgE level was over 1000 kU/l. Mean (standard deviation) UAS (Fig. 1) declined from 6.68±1.33 to 0.55±0.59 with P <0.001 from baseline (ie, the average over the

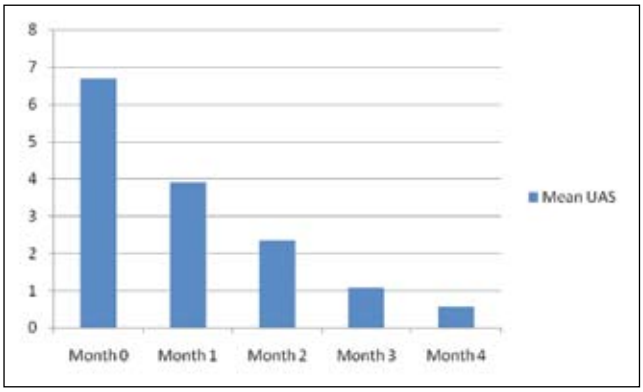

Fig. 1 Mean Urticaria Activity Score (UAS) over period of 4 months.

4-week placebo treatment period) to the final 4-week period of omalizumab treatment, which was statistically significant and clinically relevant (Table 3). Patients experienced marked reduction in UAS during the first week of omalizumab therapy and the mean UASs continued to decrease through week 16.

At the end of 4th month seven patients (58.33%) were completely symptom free without additional therapy or received only therapy when required, five patients (41.67%) continued only a regular intake of antihistamines, and there was no longer a need for immunosuppression therapy. A complete protection from wheal development was observed in 11(91.67%) patients in the final 4-weeks of treatment with omalizumab compared with 0 patients at baseline (month 0) (Table 4). Similarly, complete absence of erythema, pruritus and interference with daily activity was observed in 9 (75%), 8 (66.67%) and 9 (75%) patients, respectively, during the final 4 weeks of treatment with omalizumab compared with only 1(8.33%), 0(0%) and 1(8.33%) patients, respectively, at the baseline (Figs. 2,3,4). The use of rescue medication was significantly (P<0.05) reduced from 3.87±0.56 tablets at baseline to 0.48±0.36 tablets during the final 4-week period of omalizumab treatment.

Adverse Side effects were recorded in four patients (33.33%) in the form of fatigue, mild reduction in blood pressure and intermittent headache during the first few days after injection of omalizumab. All patients were followed up for 6 month after they had finished omalizumab, and there were no reports of reappearance of urticaria symptoms or of other adverse effects.

Table 3 Urticaria activity score during treatment period with omalizumab.

Patient	Month 0	Month 1	Month 2	Month 3	Month 4
Patient 1	5.20	3.54	2.91	2.13	1.55
Patient 2	7.63	4.25	2.16	0.82	0.50
Patient 3	5.17	3.65	1.58	1.02	0.26
Patient 4	6.54	3.18	1.11	0.47	0
Patient 5	5.50	2.97	1.62	1.00	0.83
Patient 6	4.93	3.37	2.81	2.07	1.61
Patient 7	7.29	4.59	2.34	0.86	0.37
Patient 8	8.32	4.18	3.05	0.27	0.11
Patient 9	8.67	5.11	2.76	0.71	0
Patient 10	6.51	3.94	1.86	0.52	0
Patient 11	8.18	4.88	3.09	1.58	0.23
Patient 12	6.23	3.27	2.85	1.44	1.10

Table 4 No. of wheels score, at baseline and after omalizumab monotherapy

Score	Baseline# No. of patients (%)	OMZ * No. of patients (%)
None (0)	0(0)	11(91.67)
<10 (1)	2(16.67)	1(8.33)
10-50 (2)	6(50)	0(0)
>50 (3)	4(33.33)	0(0)

during 4-week placebo treatment period

*during final 4-week period of omalizumab monotherapy

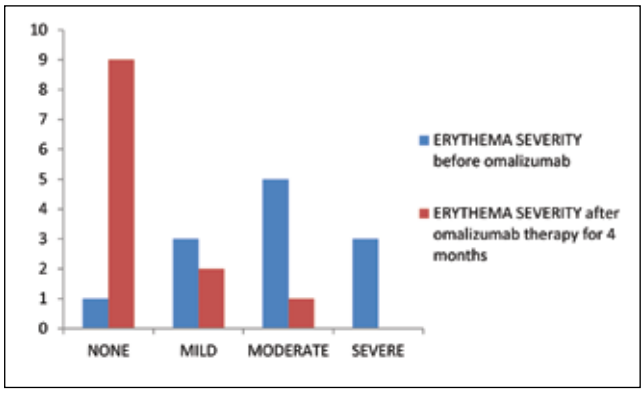

Fig. 2 Erythema severity.

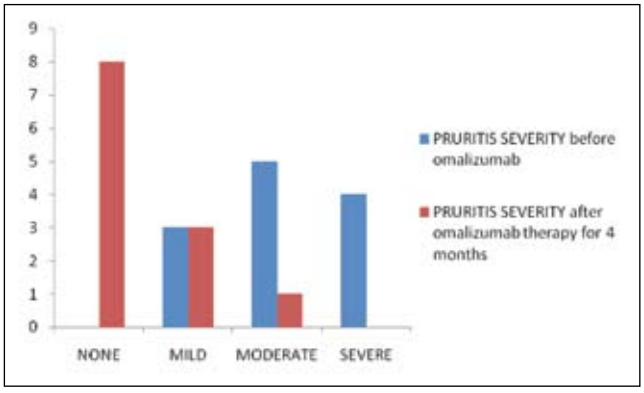

Fig. 3 Pruritis severity.

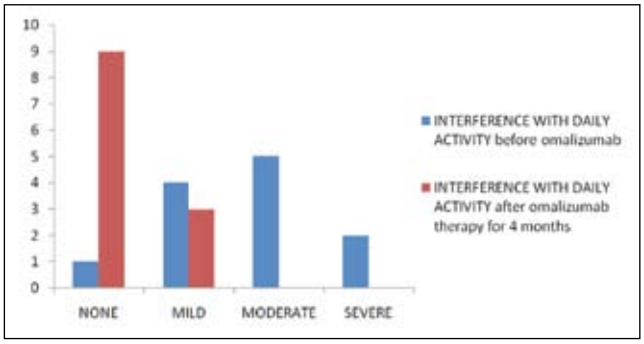

Fig. 4 Interference with daily activity.

DISCUSSION

Use of omalizumab in patients with refractory CIU has been recently reported in the medical literature.[23,24,25] Majority of them are case reports involving few patients. The results of our study showed that omalizumab is effective in moderate to severe refractory CIU and significantly reduced the disease activity and need for additional medication. In our study, in addition to significant reduction in UAS, omalizumab resulted in complete protection against the appearance of wheals in 91.67%. Similar observation was made with regard to erythema, pruritus and interference with daily activity, leading to significant amelioration of the disease experience and decreasing the burden and side effects of additional medication.

A rapid onset of action was noted for omalizumab in the treatment of refractory CIU with a rapid decrease in UASs observed during the first week of therapy as obtained from daily UAS scores recorded by the patient. The declining UAS score trend continued until the end of study. This rapid initial improvement in disease activity was observed in previous studies[22,26] as well as significant clearing of urticaria within 1 week of starting omalizumab therapy was reported by Spector and Tan[25] in patients with refractory CIU who had earlier received different combinations of antihistamines, antileukotrienes, H2-blockers, and lipoxygenase inhibitors with little or no success. This observation contrasts with the experience gained with omalizumab in the treatment of moderate-to-severe allergic asthma, in which 16 weeks of treatment are recommended to demonstrate clinical response.[27] Treatment effects of Omalizumab occur usually in 8 to 10 weeks in asthma and rhinitis concomitant with reduction of bound IgE and IgE receptors.[28] Patients with CIU have lower levels of serum IgE relative to patients with asthma, and there is little information supporting the relationship between serum IgE levels and CIU. The mechanism by which omalizumab might be working in these cases is not clear because they do not appear to be IgE-mediated events.[29] Additionally, omalizumab has been shown to produce immune-modulating effects beyond IgE and its receptors, including

effects on peripheral eosinophil and T-lymphocyte function.[15,16,28] It has been postulated that the mechanism of action for omalizumab might be through a more direct effect on mast cell/basophil reactivity that would reduce hive generation relatively quickly instead of requiring the long-term change in the steady-state levels of serum IgE necessary for asthma control.[22]

Saavedra and Sur observed significant improvement after the first treatment with omalizumab, in their CIU patient being treated with cyclosporine (200mg daily in divided doses). Though it was 14 weeks until they were able to completely withdraw the patient from cyclosporine use altogether. It might be due to a slower response for achieving a decrease in mast cell numbers, mast cell function and/or mediator release. Indeed, regulation of mast cell survival is thought to be mediated in part by IgE-FcεRI dependent pathways.[30] Effect on mast cell survival might be responsible for the continued slower response after the initial rapid response as observed in our study as well as the previous studies.[22,26] CIU involves a number of mechanisms in addition to IgE fCR autoantibodies. For example, potential interaction with thyroid autoimmunity and the coagulation pathway may alter mast cell activation.[8,31] Two patients in our study had thyroid autoimmunity along with CIU and responded to omalizumab treatment supporting another study of its efficacy in such patients.[26]

The use of omalizumab was associated with overall reduction in the use of rescue medication from 3.87 tablets at baseline to 0.48 daily at the end of treatment. This is in consistency with previous studies by Maurer et al[26] and Kaplan et al.[20] The frequency of use of rescue medication for symptomatic relief provides an indication of the degree of clinical impairment.[25] Hence, omalizumab resulted in decrease in the clinical impairment as well as burden of the repeated use of rescue medication. In this study, mean UAS decreased significantly, mean rescue medication use declined, and the overall therapeutic response improved. This consistency in effect across all defined outcome measures, underlines the internal validity of the study and suggests that omalizumab as monotherapy, might be useful in the treatment of moderate to severe refractory CIU not responding to any other therapeutic option. No new safety concerns regarding laboratory parameters or clinically relevant vital signs were observed in our patients treated with omalizumab for CIU. The limitations of this study were a small cohort of patients and absence of placebo controlled comparable parallel-group. Although patients were blind to treatment sequence, investigators were aware. Among its strengths are assessment of effect after placebo exposure to establish a baseline, close follow-up based on specialist care and most importantly, outcome measures were primarily patient- reported enhancing the external validity of the study.

CONCLUSION

Thus omalizumab has shown promise and is increasingly becoming an accepted immunosuppressive sparing new treatment modality for refractory CIU patients with disease burden that is difficult to manage otherwise. In addition, omalizumab had a good overall safety and tolerability profile in our patients. The results of this study support the use of omalizumab in treating moderate to severe refractory CIU, in consis-

tency with the latest version of the European Academy of Allergy and Clinical Immunology/ Global Allergy and Asthma European Network/ World Allergy Organization/European Dermatology Forum guidelines,[9] which recommend omalizumab as a treatment option for patients with CIU whose disease is refractory to standard therapies. Further studies including larger number of patients, having double blind placebo- controlled design and studies that involve variation in frequency and duration of treatment should be conducted to establish role of omalizumab in refractory CIU.

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