

Original Research Article

Omalizumab in chronic spontaneous urticaria

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Received: 03 June 2018

Accepted: 11 July 2018

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ABSTRACT

Background: Chronic spontaneous urticaria is a common skin disorder affecting 0.5 to 1% of people in the general population. There are a variety of treatment options available without much successful outcome. Omalizumab is a novel treatment option which can be used in the treatment of chronic spontaneous urticaria. The aim of our study is to assess the efficacy of omalizumab in chronic spontaneous urticaria.

Methods: A retrospective analysis of data of 10 patients with chronic spontaneous urticaria who were treated with three doses of omalizumab in our institution. Doses were given at monthly intervals for 3 months and they were followed for another 6 months. Response was assessed using Urticaria Activity Score.

Results: 70% of patients had well controlled urticaria with 3 doses of omalizumab by the end of 9 months.

Conclusions: Omalizumab is a safe and effective treatment option in the management of chronic spontaneous urticaria.

Keywords: Chronic spontaneous urticaria, Urticaria Activity Score, Omalizumab

INTRODUCTION

Urticaria is a distressing dermatoses characterized by transient itchy erythematous wheals. Chronic spontaneous urticaria (CSU) is known to be the most common form of chronic urticaria, but there are few robust data on the exact prevalence of it.¹ The reported life time prevalence for urticaria is 7.8% to 22.3% and the point prevalence for CSU is 0.5% to 1%.^{1,2} Statistical analysis of patients presenting with chronic urticaria suggests 66 to 93% of cases are CSU, 4 to 33% of cases are physical urticaria and 1 to 7% of cases are cholinergic urticaria.¹ The exact prevalence of CSU in India is not known.³ Chronic spontaneous urticaria is characterized by the spontaneous daily or almost daily occurrence of itchy wheals, angioedema or both for more than or equal to 6 weeks with no obvious cause.^{1,4} CSU is a chronic disease whose duration is estimated to be 1 to 5 years.^{1,5} Of the diagnosed CSU patients, 50% will resolve within 6

months of onset, 20% will resolve within 3 years, 20% will resolve within 5 to 10 years and less than 2% will resolve within 25 years.⁵ In very rare cases it can persist for up to 50 years.¹ It is almost twice as common in females as males with peak incidence at 20 to 40 years of age. It has an unpredictable course that can have a profoundly negative impact on patient's quality of life as well as a high socioeconomic impact.⁶ Dermatology Life Quality Index (DLQI) scores for CSU ranges from 9.3 to 14. They have poorer quality of life when compared to other dermatological conditions.⁷

Although the pathogenesis of CSU is not fully understood, aberrant release of histamine and other inflammatory mediators by mast cells and basophils is thought to play a central role.^{8,9} EAACI/GA²LEN/EDF/WAO guidelines state that urticaria is a mast cell-driven disease.⁴ Mast cell activation in CSU may be via autoimmune, allergic or

idiopathic mechanisms.¹⁰ As such CSU is thought to have either autoimmune or idiopathic cause. Approximately 45% of autoimmune CSU patients have antibodies directed against IgE receptor or IgE itself and 33% of patients have IgE anti-thyroperoxidase autoantibodies.^{10,11} Although CSU is not believed to have an allergic basis, total IgE levels are generally high when compared to healthy controls.^{12,13} IgE binds to high affinity receptor FcεR1 on mast cells, basophils and eosinophils. Cross-linking of surface IgE by antigen leads to mast cell or basophil degranulation and release of histamine and other inflammatory mediators. Omalizumab is a monoclonal humanized IgG1κ antibody against IgE antibody that binds to free IgE and prevents its attachment to FcεR1 and downregulates its expression on basophils, mast cells and eosinophils.¹⁵⁻¹⁸ The recent EAACI/GA²LEN/EDF/WAO guidelines have updated the CSU diagnostic steps which includes thorough history about the time of onset, frequency, duration and provoking factors for hives and/or angioedema.⁴

Though CSU is the most likely diagnosis in patients with recurrent hives and angioedema, the following differential diagnosis should be kept in mind which includes Schnitzler's syndrome, systemic onset juvenile idiopathic arthritis, adult onset Still's disease, Muckle-Wells syndrome, TNF receptor alpha associated periodic syndromes. Hereditary and acquired angioneurotic angioedema and ACE inhibitors induced angioedema should be ruled out before diagnosing them as CSU.⁴ The current European Academy of Allergy and Clinical Immunology (EAACI) treatment guidelines recommend modern second generation H₁ antihistamines as first line therapy. If there is no response after 2 weeks of therapy, then increase the dosage upto fourfold of modern second generation antihistamines as second line treatment. Third line treatment include omalizumab, cyclosporine and montelukast as add on therapy.⁴ Only few studies are available regarding the omalizumab therapy in CSU because of high cost of therapy. We hereby present our experience with omalizumab in the management of CSU.

This study aimed to determine the efficacy of three doses of omalizumab in the management of chronic spontaneous urticaria.

METHODS

We retrospectively analysed the data of 10 patients with chronic spontaneous urticaria treated with 3 doses of omalizumab in the Department of Dermatology, Madras Medical College, RGGGH from September 2016 to September 2017. Patients were evaluated completely at the first visit which included detailed history and laboratory workup.

Baseline investigations like complete hemogram with differential, absolute eosinophil count, ESR, CRP, liver and renal function tests, ELISA for HIV 1 and 2 antibody, VDRL, stool for parasites, thyroid function test,

anti-thyroglobulin antibody, autologous serum skin test, chest X-ray, ECG, hepatitis B and C, antinuclear antibody test, cryo-agglutinins, tryptase and complement levels were carried out. All the results were within the normal range. Three doses of omalizumab were given at 4 weekly intervals. All the patients were admitted for every dose of omalizumab and monitored for 2 hrs post injection to look for adverse effects, especially anaphylaxis. Patients were taught regarding how to carry out Urticaria Activity Score (UAS7) (Table 1) at the initial visit and insisted them to perform regularly during each follow up visit. Patients were reviewed every 2 weeks, during which disease symptoms and severity were assessed using UAS score and they were followed till 36 weeks. Patients were advised to take tablet cetirizine 10 mg on required basis only. Mast cell stabilizers, H₂ blockers, steroids and adjuvant immunosuppressants were avoided during the study period.

Table 1: Urticaria Activity Score.

UAS7	Severity classification	Severity details
28-42	Severe CSU	Typically with intense itch and more than 50 hives over 24 hours or large confluent areas of hives.
16-27	Moderate CSU	Typically with a troublesome itch and up to 50 hives over 24 hours.
7-15	Mild CSU	Typically with a mild itch and fewer than 20 hives over 24 hours.
1-6	Well-controlled CSU	Typically with a mild itch and no hives or fewer than 20 hives over 24 hours.
0	Itch- and hive-free	Over 7 days

UAS7: Weekly Urticaria Activity Score; CSU: Chronic spontaneous urticaria.

Inclusion criteria

Inclusion criteria were patients with chronic spontaneous urticaria of duration more than 2 yrs; age between 12 and 65 years; UAS7 more than or equal to 16; no or poor response to other treatment modalities which include antihistamines (4X approved dose of H₁ blockers), leukotriene receptor antagonist, autologous serum skin therapy.

Exclusion criteria

Exclusion criteria were age less than 12 years and greater than 65 years; pregnant and lactating woman; patient with deranged liver and renal function tests; patients with physical urticaria, urticarial vasculitis, urticaria secondary to known cause; history of epilepsy, tuberculosis, stroke, coronary artery disease.

RESULTS

At the end of 3 months, disease free rate was 60% (6/10) and well controlled urticaria was 40% (4/10). By the end of 6 months, disease free rate and well controlled urticaria were 20% and 80% respectively. At the end 9 months, 70% (7/10) had well controlled urticaria, 10% (1/10) had disease free state and 20% (2/10) had mild urticaria (Figure 1, Table 2). All the patients showed their maximum response to treatment between 16 and 20 weeks. Even at the end of 9 months the UAS7 scores were well below the baseline scores (Figure 2).

Table 2: Response to 3 doses of omalizumab.

Disease state	End of 3 months (%)	End of 6 months (%)	End of 9 months (%)
Disease free	60	20	10
Well controlled	40	80	70
Mild urticaria	-	-	20

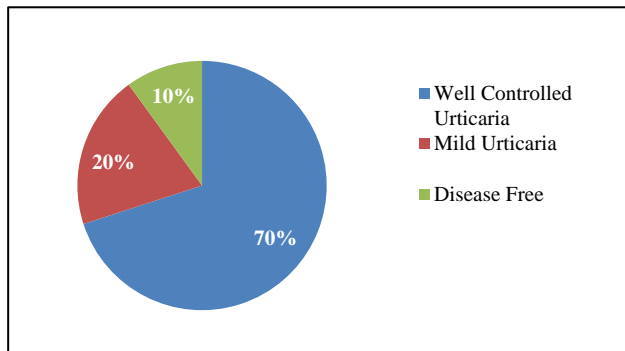


Figure 1: Response to omalizumab at the end of 9 months.

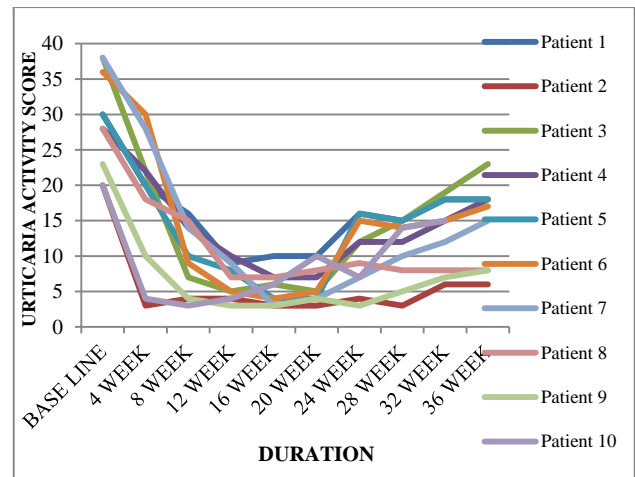


Figure 2: Urticaria Activity Score 7 over the period of 36 weeks.

DISCUSSION

In the study period, ten patients were treated with omalizumab of which 80% (8/10) were females and 20% (2/10) were males. Mean age group of the study population was 35.9 years. Duration of the disease ranged from 2 yrs to 8 yrs with the average of 5 yrs. 60% (6/10) of patients (5 females and 1 male) had associated angioedema. 20% (2/10) of patients had elevated IgE levels (>300 IU/ml). Their previous treatment modalities were oral antihistamines-both H₁ and H₂ blockers, two were treated with mast cell stabilizers additionally and two were treated with autologous serum skin therapy. Oral dapsone therapy for 6 months was given to 2 patients. There was no satisfactory response to any of the above said treatments and such patients were given 3 doses of omalizumab.

Table 3: Demographic profile.

Sl no.	Age/sex	Duration (in years)	Angioedema	IgE levels (in IU/ml)	Past treatment	Comorbidity	ASST positivity
1	37/F	8	Absent	260	Oral AH	BA	Negative
2	56/F	5	Present	73.13	Oral AH and mast cell stabilizers	DM	Negative
3	33/F	6	Present	59	Oral AH, steroids, dapsone	-	Positive
4	37/M	2	Present	372	Oral AH, steroids, dapsone	-	Negative
5	34/F	5	Present	230	Oral AH, ASST	-	Positive
6	48/F	8	Present	30.3	Oral AH and mast cell stabilizers	DM, HTN	Negative
7	40/F	2	Present	85	Oral AH, ASST	-	Positive
8	27/F	7	Absent	180	Oral AH	-	Negative
9	27/M	5	Absent	394	Oral AH	-	Negative
10	20/F	2	Absent	92	Oral AH	-	Negative

F: Female, M: Male, AH: Antihistamines, BA: Bronchial asthma, DM: Diabetes mellitus, HTN: Hypertension, ASST: Autologous serum skin test/therapy.

Comorbidities were bronchial asthma in one patient, diabetes mellitus in one patient, diabetes mellitus and hypertension together in one patient. Autologous serum skin test was positive in 30% (3/10) of the participants (Table 3).

Average UAS7 scoring before starting omalizumab in preceding week was 29.1. At the end of 3 months, 60% (6/10) of patients became disease free and 40% (4/10) of patients had well controlled urticaria. After 6 months, 20% (2/10) of patients became disease free and 80% (8/10) of patients had well controlled disease. By the end of 9 months, 70% (7/10) of patients had well controlled urticaria with 3 doses of omalizumab alone, 10% (1/10) of patients had disease free state and 20% (2/10) of patients had mild urticaria (Figure 1, Table 2).

50% (5/10) of patients achieved their maximum response to therapy at the end of 12 weeks. 50% (5/10) of patients achieved their maximum response at the end of 16 weeks. 20% (2/10) of patients became itch- and hive- free with one dose of omalizumab itself. In our study 100% (10/10) of patients responded to omalizumab in contrast to 96% response rate seen in a study conducted by Neema et al.¹⁴ All patients showed response within one month of therapy. The frequency of intake of antihistamines per week dropped to 0 in few and 1-3 in some patients. We wanted to stress the fact that the UAS7 score were well below the baseline scores at the end of 9 months (Figure-2). 3 patients maintained their initial response to therapy till the end of 9 months (Figure-2, patient number-2, 8, 9).

Side effects observed in our study were mild which include pain, redness and swelling at the injection site observed in 3 patients during 1st and 2nd injections which subsided within 1 to 2 hours and it did not recur with subsequent injections.¹⁹ Development of urticarial wheals at injection site was noted in 2 patients, during 3rd dose in one patient and 2nd dose in another patient which subsided within 4 to 5 hrs with antihistamines alone. There was no recurrence of wheals in successive doses. It is not known whether it is due to the disease itself or as a side effect of omalizumab. In Neema et al study no side effects was observed.¹⁴ Anaphylaxis was not reported in our study as in the study by Maurer et al.¹

We observed that there were no correlations between serum IgE level, age of the patient, disease duration, concomitant comorbidity and the response to omalizumab.²⁰

CONCLUSION

Thus omalizumab has a promising role in the management of chronic spontaneous urticaria which has not responded to other treatment modalities. But more studies on larger samples are required to validate our results.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Ramesh A, Sampath V, Dhanalakshmi UR, Vinitha Kumari G. Omalizumab in chronic spontaneous urticaria. *Int J Res Dermatol* 2018;4:424-8.