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An observational study on the efficacy of single injection of omalizumab in the treatment of chronic spontaneous urticaria

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Abstract

Chronic Spontaneous Urticaria (CSU) is one of the most challenging therapeutic problems faced by dermatologists. Omalizumab is a third line drug for CSU which is currently recommended as monthly injections for 6 months. To study the efficacy of single injection of Omalizumab in the treatment of CSU. This was a prospective single center observational study. Single dose of injection Omalizumab 300 mg was administered to 30 patients of CSU on double the dose of tablet Fexofenadine 180 mg with Urticaria Activity Score (UAS-7) more than 15 and their response was assessed using UAS-7 up to 6 months. The mean duration of response of early and late responders were analyzed. Of the 30 patients who completed the study, 29 patients (96.7%) were responders and one (3.3%) was nonresponder. Of the 29 responders, 21 (70%) were early responders and eight (26.7%) late responders. The mean total symptom free durations amongst early and late responders were analyzed and were found significant. The prolonged symptom free intervals in early responders after single injection of Omalizumab followed by antihistamines not only prevented over treatment with Omalizumab but was also cost saving in the long-term management of these cases. With careful monitoring of UAS7 scores an individualized, cost-effective approach can be adopted in the treatment of CSU. This study provides a basis for larger studies and may eventually determine a new standard of care with respect to limiting the doses of a biologic.

KEYWORDS

anti-IgE antibody, chronic spontaneous urticaria, omalizumab, urticaria activity score

1 | INTRODUCTION

The earliest description of urticaria is found in "The Yellow Emperor's Inner Classic", written by Huang Di Nei Jing, between 1000 and 200 BC meaning wind-type concealed rash. CSU is characterized by occurrence of wheals, angioedema or both for more than 6 months in the absence of a trigger and have an incidence of 0.5% to 1% in general population with an average duration varying from 1 to 5 years.¹ CSU patients have a poor health status and subjective well-being affecting their quality of life. Various treatment modalities like

antihistamines, steroids, dapsone, sulfasalazine, hydroxychloroquine, tricyclic antidepressants, immunosuppressive treatments in the form of intravenous immunoglobulins, rituximab, methotrexate, and mycophenolate mofetil have been tried.²

Present treatment guidelines recommend Omalizumab as a third line add on drug to the 4-fold dose of modern second generation antihistamines.² The sedative potential is the main limiting factor in up dosing up to four times the dose of antihistamines which is not generally tolerated by patients. Of the commonly used antihistamines Fexofenadine is the drug with the best sedation vs benefit ratio.³

Omalizumab is a humanized anti IgE monoclonal antibody which acts by binding to the free IgE antibodies. It also has an indirect effect by the downregulation of FcεRI receptors. Present guidelines recommend monthly injections of 300 mg Omalizumab for 6 months in refractory cases of CSU not responding to second generation anti histamines.⁴ Data on efficacy of single injection of Omalizumab is scant.⁵ If found effective in reducing the UAS-7 scores, there would be a tremendous cost saving in giving this expensive monoclonal antibody only once in 6 months.

2 | METHODS

This prospective single center observational study was carried out after obtaining institutional ethical committee clearance, amongst patients above 12 years of age diagnosed as a case of CSU and who were symptomatic with moderate to severe urticaria (UAS-7 > 15) even after two doses of Fexofenadine 180 mg in a day. Pregnant and lactating women, patients with inducible urticaria, internal malignancy, immunocompromised, those previously treated with Omalizumab and patients who were unwilling to comply with the study guidelines and follow-up were excluded.

All treatment modalities of CSU other than tablet Fexofenadine were stopped 1 month before administering injection Omalizumab. Initial UAS-7 score was recorded. The patients were administered a single dose of injection Omalizumab 300 mg subcutaneously and tablet Fexofenadine was continued till the patients were either urticaria free or well controlled (UAS7 0-6) and thereafter stopped. The patients were followed up for a period of 6 months. Those patients who became symptomatic during follow-up were prescribed up to double the dose of tablet Fexofenadine and were observed till they became moderately symptomatic (UAS-7 > 15). Patients who at any

time after the first 4 weeks of injection Omalizumab became moderately symptomatic even on double the dose of tablet Fexofenadine 180 mg were prescribed another dose of injection Omalizumab and were excluded from further study. Patients filled up the patient self-evaluation sheet and UAS-7 scores were calculated as per the evaluation sheet maintained by patient at serial intervals.

The response to treatment was assessed at fixed intervals during therapy and patients were classified as:

1. Responders: all patients who showed reduction in UAS-7 score at 4 weeks of injection.
2. Early responders: responders with more than 20% reduction in UAS-7 score from baseline within 8 days of injection
3. Late responders: responders with <20% reduction in UAS-7 score from baseline after 8 days of injection
4. Nonresponders: patients with no reduction in UAS-7 scores at 4 weeks of therapy.
5. Complete response: Patient is asymptomatic with single dose of Omalizumab alone.
6. Partial response: Patient requires tablet Fexofenadine in addition to single dose of Omalizumab to be asymptomatic.

UAS7 were assessed based on the patient self-evaluation sheet at initiation of therapy, 01, 02, 03, 04, 08, 12, 16, and 24 weeks. (Figure 1, Strobe statement).

3 | STATISTICAL ANALYSIS

The mean duration for initial response, duration for complete response and total duration symptom free or mildly symptomatic with fexofenadine were compared between early responders and late

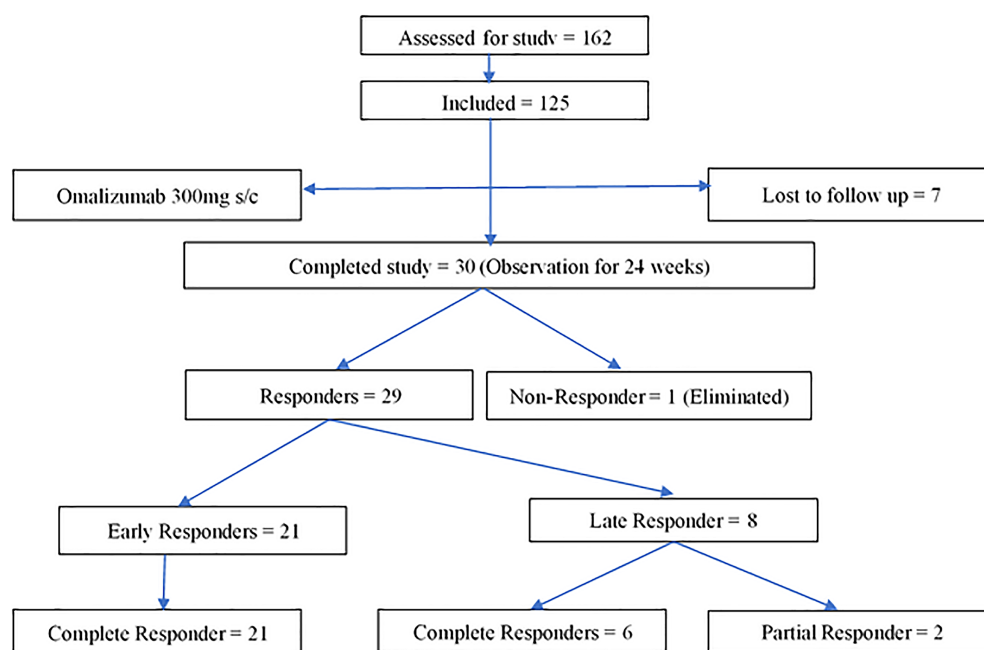


FIGURE 1 Strobe statement

TABLE 1 Demographic profile

Characteristics	Study group	Early responders (n = 21)	Late responders (n = 8)	Non responders (n = 1)
Average age years (SD)	36.83 (11.98)	38.28 (11.18)	35.12 (13.71)	20
Male	19 (63.33)	8 (38.1)	5 (62.5)	1
Female	11 (36.66)	13 (61.9)	3 (37.5)	Nil
Duration of disease, months (SD)	28.93 (38.94)	29.61 (43.56)	27.75 (31.08)	24
UAS-7 average (SD)	33.5 (3.36)	33 (3.43)	34.5 (3.2)	36
Angio-oedema	1 (3.3)	1 (4.76)	Nil	Nil
Hypothyroidism	7	0	6	1
Anti TPO	5	2	2	1

TABLE 2 Study response amongst various groups

Characteristics	Study group	Responders (n = 29)	Early responder (n = 21)	Late responder (n = 8)	Sig (2-tailed)
Initial response (days)	7.55 (6.25)	7.55 (6.25)	4.14 (1.19)	16.5 (5.09)	.000
Complete response (days)	12.63 (9.66)	12.04 (9.67)	8.23 (3.36)	21 (14.89)	.001
Total duration symptom free or mildly symptomatic on antihistamines	117.46 (65.32)	121.51 (62.74)	138.61 (55.27)	41.62 (36.94)	.000

responders and their statistical significance were analyzed using "independent samples student *T* test".

4 | RESULTS

A total 162 patients were assessed for the study over a period of 18 months of which 125 patients were excluded based on exclusion criteria and seven were lost to follow-up. 30 patients completed the study. Of the 30 patients, 29 patients (96.7%) were responders and one patient (3.3%) was nonresponder (Figure 1). Of the 29 responders, 21 (70%) were early responders and eight (26.7%) were late responders. The clinico-demographic characteristics of the study population are as per (Table 1). There was no correlation with the age, sex, and duration of disease with the severity and response to treatment. Seven patients were found to have hypothyroidism of which six were late responders and one was non responder. Five patients had Anti TPO positivity of which two were early responders, two were late responders and one was non responder. The patients had taken various treatments for chronic urticaria including anti-histamines, mast cell stabilizers, varying courses of steroids, Dapsone, Cyclosporine, and Methotrexate. The average UAS-7 scores were 33.5 (SD 3.36), 36, 33 (SD 3.43), and 34.5 (SD 3.2) that of study population, nonresponders, early responders and late responders, respectively.

Three patients were excluded from the study at 1 month after administration of injection as they attained UAS7 > 15 even on double the dose of Tab Fexofenadine 180 mg on follow-up. Only four (13.3%) patients remained asymptomatic or mildly symptomatic for a duration of 6 months after a single dose of injection Omalizumab.

The mean duration of initial response of early and late responders were analyzed and was found to be significant. All 21 early responders attained complete response while amongst the late responders only six attained complete response. The period to achieve complete response of early and later responders were analyzed and found significant. The mean total durations symptom free or mildly symptomatic with anti-histamines amongst early and late responders were analyzed and were found to be significant (Table 2). No adverse effects were noted in the study population.

5 | DISCUSSION

CSU is a common disease that is particularly difficult to treat and in severe cases the impact it has on the health related quality of life is comparable to that of a coronary artery disease patients.⁶

Omalizumab is an anti IgE antibody approved as a third line drug for treatment of CSU. There is no specific guideline for the use of Omalizumab in CSU, though most recommendations suggest the administration of Omalizumab every 4 weeks for 6 months. Serum IgE levels in urticaria and response to Omalizumab was not found to be variable in earlier studies and so was not assessed in the present study.⁷

The present study assessed the efficacy of single dose of injection Omalizumab in treatment of CSU and followed up to a period of 6 months. A total of 162 patients were assessed of which 30 patients completed the study. Zuber et al⁸ in their study on epidemiology of urticaria found out that lifetime prevalence for CSU was 1.8%, and 70.3% of the subjects were female. This study population comprised of 11 (36.66%) females and 19 (63.33%) males. All though urticaria

occurs in all age groups, the peak incidence has been noted in age group between 20 and 40 years as noted by Zuber et al.^{1,8} The average age of the study population was 36.83 (SD 11.98) years with the majority falling between 18 and 40 years of age which is similar to other studies.

The average duration of CSU varies from 1 to 5 years in various studies.^{1,8,9} The average duration of disease was 28.93 (SD 38.94) months amongst the study population which was in concordance with the other studies.

The prevalence of positive thyroid autoantibodies ranged from 12% to 29% in patients with CSU in different studies.¹⁰ Prevalence of antithyroid antibodies in the present study was 16% and was equally found in early and late responders. The early responders with antithyroid antibodies were euthyroid. Seven of the 30 (23%) patients had raised TSH values. A study by Sanchez et al found out an increased incidence of Anti TPO IgE antibodies in CSU patients and IgG Anti TPO antibodies in other autoimmune thyroid disorders.¹¹ The presence of IgE Anti TPO antibodies could be the reason for early response in two patients despite antibody positivity though detailed analysis of type of antibodies were not studied.

In a study from India which has observed four patients of CSU treated with a single injection of Omalizumab and observed for a duration of 24 weeks revealed a sharp decline in UAS7 in 7 to 10 days which was maintained up to 16 weeks in one case and 20 weeks in the other three cases.⁵

In the present study of the 30 patients, 29 were responders while one did not show any improvement in urticaria symptoms at the end of 4 weeks. Of the 29 responders, 21 were early responders and eight were late responders.

The response of early responders was compared with that of late responders. The mean durations for initial response, complete response, symptom free intervals with and without anti-histamines, and mild symptomatic period with anti-histamines and total symptom free duration of the two groups were analyzed and were found to be significant. (*t* value < 0.05). No adverse effects were noted in the study population. These observations are in concordance with the only study which has observed the patients for 24 weeks after single injection of Omalizumab.⁵

In this study, it has been observed that the response rate and duration of response to Omalizumab has been better than other studies.¹² Most of the patients who responded early had a longer duration of remission of symptoms. The late responders either were not completely asymptomatic or had shorter asymptomatic periods. Moreover, they had early recurrence of symptoms and less response to anti-histamines.

The mechanism of action of Omalizumab in urticaria is not completely understood. Omalizumab acts by binding to the free IgE antibodies with an indirect effect by the down regulation of FcεRI receptor density on basophils and cutaneous mast cells, preventing activation by autoantibodies. This down regulation of receptors may be the reason for the late response of Omalizumab. The late response has been observed as late as 26 days from the date of administration of the drug. Omalizumab also stabilizes the mast cells and reduces the

sensitivity of mast cells to antigens. It also worth noting that Omalizumab therapy is a symptomatic treatment, and symptoms almost invariably recur when therapy is stopped.

Based on the above observations we recommend that administration of injection Omalizumab should be individualized to suit the needs of the patient. Early responders were found to have a longer duration of symptom free response ranging up to 6 months and hence its recommended that instead of administering Omalizumab every 4 weeks, it can be administered on "requirement" basis. The prolonged symptom free intervals in early responders after single injection followed by antihistamines not only prevented over treatment with Omalizumab but also was cost saving in the long-term management of these cases. With careful monitoring of UAS7 scores an individualized, cost-effective approach can be adopted in the treatment of CSU with Omalizumab. This study provides a basis for larger studies and may eventually determine a new standard of care with respect to limiting the doses of a biologic.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

V. Sandeep Lal: Conceptualization, Investigation, Data curation, Writing-original draft. Sandeep Arora: Investigation, Writing-review & editing. Rajeshwari Dabbas: Supervision, Writing-review & editing. Manasa Shettisara Janney: Investigation, Data curation, Writing-original draft. J. B. Sushma: Supervision, Writing-review & editing. Niyor M. Das: Supervision, Writing-review & editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Weller K, Altrichter S, Ardelean E, et al. Chronic urticaria. Prevalence, course, prognostic factors and impact. *Hautarzt*. 2010;61:750-757.
2. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393-1414.
3. Church M, Church D. Pharmacology of antihistamines. *Indian J Dermatol*. 2013;58:219-224.
4. Godse K, Rajagopalan M, Girdhar M, et al. Position statement for the use of omalizumab in the management of chronic spontaneous urticaria in Indian patients. *Indian Dermatol Online J*. 2016;7:6-11.
5. Subramaniyan R, Chopra A. Treatment of chronic spontaneous urticaria with a single dose of omalizumab: a study of four cases. *Indian J Dermatol*. 2016;61:467.
6. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol*. 1997; 136:197-201.

7. Uysal P, Eller E, Mortz CG, Bindslev-Jensen C. An algorithm for treating chronic urticaria with omalizumab: dose interval should be individualized. *J Allergy Clin Immunol*. 2014;133:914-915.e2.
8. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey: epidemiology of urticaria: a representative cross-sectional population survey. *Clin Exp Dermatol*. 2010;35:869-873.
9. Khan S, Maitra A, Hissaria P, et al. Chronic Urticaria: Indian context—challenges and treatment options. *Dermatol Res Pract*. 2013;2013:1-8.
10. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol*. 2012;129:1307-1313.
11. Sánchez J, Sánchez A, Cardona R. Causal relationship between anti-TPO IgE and chronic urticaria by in vitro and in vivo tests. *Allergy Asthma Immunol Res*. 2019;11:29-42.
12. Tonacci A, Billeci L, Pioggia G, Navarra M, Gangemi S. Omalizumab for the treatment of chronic idiopathic Urticaria: systematic review of the literature. *Pharmacother J Hum Pharmacol Drug Ther*. 2017;37:464-480.

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