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Treatment of Chronic Spontaneous Urticaria with a Single Dose of Omalizumab: A Study of Four Cases

[Radhakrishnan Subramaniyan](#) and [Ajay Chopra](#)

From the Department of Dermatology, Command Hospital Air Force, Bengaluru, Karnataka, India

Address for correspondence: Dr. Radhakrishnan Subramaniyan, Department of Dermatology, Command Hospital Air Force, Old Airport Road, Bengaluru - 560 007, Karnataka, India. E-mail: drskskin@gmail.com

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Abstract

Background:

Chronic spontaneous urticaria (CSU) has a detrimental effect on patients' emotional and physical quality of life. Omalizumab, an anti-immunoglobulin E humanized monoclonal antibody, has been shown to be very effective in the treatment of refractory chronic urticaria patients but may not be an economically viable option for all CSU patients. However, we present a case series where a single dose of omalizumab gave sustained relief of symptoms in patients with CSU, which may be an economical option.

Aims:

The aim of this study is to assess the efficacy of a single dose of omalizumab in the treatment of CSU. **Materials and Methods:** Four patients of CSU whose disease was not controlled with four times the licensed dose of tablet fexofenadine 180 mg were exhibited one subcutaneous injection of omalizumab and were followed up at 4 weekly intervals for 24 weeks for Weekly Urticaria Activity Score 7 (UAS7) and Dermatology Life Quality Index (DLQI).

Results:

A sharp decline in UAS7 and DLQI was documented in 7–10 days. The decline was maintained up to 16 weeks in one case and 20 weeks in the other three cases. Both the scores at the end of the follow-up period of 24 weeks were better than the pre-omalizumab scores.

Conclusion:

The results of this case series indicate the efficacy of a single-dose omalizumab in treating moderate to severe refractory CSU. Further studies are required to identify the minimum frequency of administering omalizumab to effectively control CSU. This would greatly reduce the cost of this novel therapy.

Keywords: *Chronic spontaneous urticaria, Dermatology Life Quality Index, omalizumab, Urticaria Activity Score 7*

Introduction

What was known?

Monthly injections of omalizumab are approved as the third-line management in moderate to severe chronic spontaneous urticaria.

Chronic spontaneous urticaria (CSU) is a debilitating skin condition characterized by the spontaneous appearance of wheals, angioedema, or both occurring intermittently or continuously for more than 6 weeks due to known or unknown causes.[1] It impacts millions of patients worldwide. CSU is thought to have the most impact on quality of life of any allergic disease and is similar in severity to triple-vessel coronary artery disease.[2,3] The condition generally has a prolonged duration of 1–5 years, persisting for more than 5 years in 11–14% of patients[4] and has a detrimental effect on patients' emotional and physical health-related quality of life.[5,6]

Omalizumab, an anti-immunoglobulin E (IgE) humanized monoclonal antibody, has now been shown to be very effective in the treatment for CSU, in case reports, case series, as well as in double-blind, placebo-controlled studies, in antihistamine refractory chronic urticaria patients.[1,7,8,9,10,11,12,13] At present, it is being recommended as the third-line treatment option in the management of CSU by the European Academy of Allergy and Clinical Immunology (EAACI).[1] It is felt that omalizumab may not be an economically viable option for all CSU patients.[14] However, we present a case series where a single dose of omalizumab gave sustained relief of symptoms in patients with CSU, which may be an economical option.

Materials and Methods

Four patients with CSU whose disease was not controlled with up to four times the licensed dose of tablet fexofenadine 180 mg, and out of which two patients also did not show a good response to cyclosporine A, were treated off-label with a single dose of 300 mg omalizumab. At the initial visit, complete history, physical examination, and clinical assessment of urticaria and angioedema were done. Laboratory evaluations included complete blood count, erythrocyte sedimentation rate, liver function test, kidney function test, stool evaluation for parasites, thyroid function test, anti-thyroglobulin antibody, total IgE, and autologous serum skin test. In addition, electrocardiogram, chest X-ray, hepatitis B and C serologies, HIV 1 and 2 antibodies, antinuclear antibody test, cryo-agglutinins, and complement levels were also carried out. All the results were within the normal range or negative. Physical urticarias, urticarial vasculitis, pregnancy, lactation, renal dysfunction, history of epilepsy, malignancy, and stroke were ruled out.

A 2-week screening period was used to confirm Urticaria Activity Score 7 (UAS7) and Dermatology Life Quality Index (DLQI) (ranging from 0 to 30, with higher scores indicating a worse quality of life). All patients maintained a daily diary to record urticarial signs and symptoms based on a scoring system [Table 1].[13] None of the patients had satisfactory response to a maximal dose (four times the licensed dose) of H1-blocker therapy. The patients were also exhibited short courses of tablet prednisolone 30 mg/day for a week whenever they had acute exacerbations as per guidelines.[1]

Thereafter, patients were gradually weaned off other medication excluding H1-blockers 4 weeks before the administration of omalizumab. At the end of this 4-week period, a single dose of 300 mg was administered as a subcutaneous injection with necessary precautions to handle possible anaphylaxis and other adverse effects.

Patients were then followed up at 4 weekly intervals over 24 weeks. Daily records for urticaria signs and symptoms were maintained throughout the follow-up period. The response to treatment was assessed at these visits based on the weekly UAS7 and DLQI during each visit. Patients were permitted to take 180 mg fexofenadine on required basis. The use of fexofenadine was tabulated at each visit.

Results

We treated four patients with moderate to severe refractory CSU with a single dose of 300 mg omalizumab at the Department of Dermatology, Command Hospital Air Force, Bengaluru, and followed them up over 6 months. Informed consent was obtained from all the patients before starting the treatment. Patient demographics and clinical characteristics are summarized in Table 2.

There was a significant improvement in all the four patients. After the initial 7–10 days, a sharp decline in UAS7 and DLQI was documented. This decline was maintained for the next 16 weeks when Case 3 first showed relapse of urticaria with UAS7 increasing followed by the other three patients relapsing at 20 weeks. The UAS7 and DLQI over the follow-up period are shown in Tables 3 and 4, respectively. Both the scores at the end of the follow-up period of 24 weeks were better than the pre-omalizumab scores.

During the entire follow-up period, the patients were managed only with tablet fexofenadine 180 mg on required basis. No adjuvant immunosuppressants were prescribed. Case 3 suffered from a single episode of an acute flare at 20 weeks which was managed with a short course of oral prednisolone as per guidelines.[1] However, no attacks of angioedema were observed in Case 3 in the follow-up period. Apart from a mild transient injection site reaction in Case 1, no other adverse reactions of the drug were observed.

Discussion

Omalizumab is effective in CSU of doses from 150 to 300 mg/month as per the EAACI 2013 guidelines.[14] We wanted to assess the efficacy of a single dose of 300 mg omalizumab, in patients with severe chronic urticaria not responding to recommended therapies and often requiring systemic steroids to control exacerbations. It was observed that omalizumab had a rapid onset of action in the treatment of refractory CSU with a rapid decrease in UAS7 within 2 weeks of administration. This rapid response and decline in UAS7 are in agreement with that observed in previous studies.[15,16] The declining UAS7 trend continued till the end of 24 weeks follow-up period [Figure 1].

The DLQI showed a correlation with the UAS7. A marked improvement was observed within the first 2 weeks and the response was sustained till the end of 24 weeks period [Figure 2].

We would like to highlight the fact that both the UAS7 and DLQI at 24 weeks were below the baseline scores. Moreover, post-omalizumab, the urticarial episodes became more responsive to tablet fexofenadine and overall reduction in the use of rescue medication was noted. The frequency of intake of fexofenadine dropped to 1–2 tablets of fexofenadine 180 mg/week.

Case 3 was the first patient to show a return of urticarial lesions at 16 weeks. It is interesting to note that this patient's IgE level was the lowest among all the patients prior to omalizumab. Since omalizumab is an anti-IgE antibody, this patient whose IgE levels were the least probably showed the weakest response to omalizumab. Although raised IgE levels are not mandatory for administration of omalizumab in CSU unlike in bronchial asthma where the dosage of the drug is dependent on IgE levels,[1] it is possible that patients of CSU whose IgE levels are normal have other mechanisms causing the urticaria and so may not benefit as much as patients with high-IgE levels.

The mechanism by which omalizumab improves urticaria has not been fully elucidated. It has been reported that patients with active CSU have abnormal basophil function, including suppression of the high-affinity IgE receptor (Fc ϵ RI) pathway (related to altered expression of src homology 2 – containing inositol phosphatase), blood basopenia, and recruitment of basophils to skin-lesion sites. In patients with CSU in remission, blood basopenia and suppressed Fc ϵ RI function revert toward normal.[17] Effect on mast cell survival might be responsible for the continued slower response after the initial rapid response as observed in our cases as well as the previous studies.[15,18]

Although omalizumab is increasingly becoming a widely accepted treatment modality for refractory CSU patients, the high cost of the recommended regimen of monthly dosing curbs its use in the Indian scenario. However, as is evident from our experience, even a single dose of 300 mg omalizumab is sufficient to produce significant remission and decrease in UAS7 and usage of rescue medication in patients with refractory CSU. This translated into a better overall therapeutic response and a substantial improvement in the DLQI.

We recommend that randomized control trials can be carried out to assess the minimum effective frequency of injection omalizumab which is required to achieve disease remission and thereafter, maintain the improved UAS7 scores and DLQI using conventional medication. This would make this novel therapy more accessible to the patients who need it the most.

Conclusion

The results of this study of four cases indicate the efficacy of a single-dose omalizumab in treating moderate to severe refractory CSU. The limitation of this study is that it is only a case series of four cases. Further randomized controlled trials on larger samples are required to identify the minimum frequency of administering omalizumab to effectively control CSU. This would greatly reduce the cost of this novel therapy.

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Conflicts of interest There are no conflicts of interest.

What is new?

- Even a single dose of omalizumab gives sustained improvement in chronic spontaneous urticaria (CSU) with lowering of the Urticaria Activity Score 7 and Dermatology Life Quality Index up to 24 weeks
- More studies will be required to determine the minimum frequency of dosing with omalizumab for it to be both economical and effective in CSU.

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Figures and Tables

Table 1

Score *	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

*Sum of score: 0-6 for each day is summarized over 1 week
(maximum 42)

The Urticaria Activity Score 7 for assessing disease activity in chronic urticaria

Table 2

Patient particular			Urticaria characteristics							
Number	Age/sex	Type	Duration (years)	Angioedema	ASST	IgE (IU/mL) 1.5-378.0	Previous treatment	UAS7 before injection	DLQI before/ injection	Side effect
1	41/female	CSU	5	-	Negative	750.4	H1*, H2†, Pred‡, CsA§	20	20	Injection site reaction
2	20/male	CSU	2	-	Negative	578.5	H1, H2, Pred	30	21	Nil
3	40/male	CSU	2	+ two episodes	Negative	68.5	H1, H2, Pred	36	24	Nil
4	45/male	CSU	3	-	Negative	630.5	H1, H2, Pred, CsA	34	24	Nil

[‡]Prednisolone, [§]Cyclosporine A, ^{*}H1: Antihistamine, [†]H2: Antihistamine, CSU: Chronic spontaneous urticarial, UAS7: Urticaria Activity Score 7, DLQI: Dermatology Life Quality Index, ASST: Autologous Serum Skin Test, IgE: Immunoglobulin E, +History of Angioedema present

The demographic and clinical characteristics of the patients

Table 3

Case number	UAS7					
	Baseline (pre-omalizumab)	4 weeks	8 weeks	16 weeks	20 weeks	24 weeks
1	20	0	0	0	8	8
2	30	0	0	0	4	8
3	36	0	0	4	8	6
4	34	0	0	0	4	4

UAS7: Urticaria Activity Score 7

Urticaria Activity Score 7 over 24 weeks follow-up period

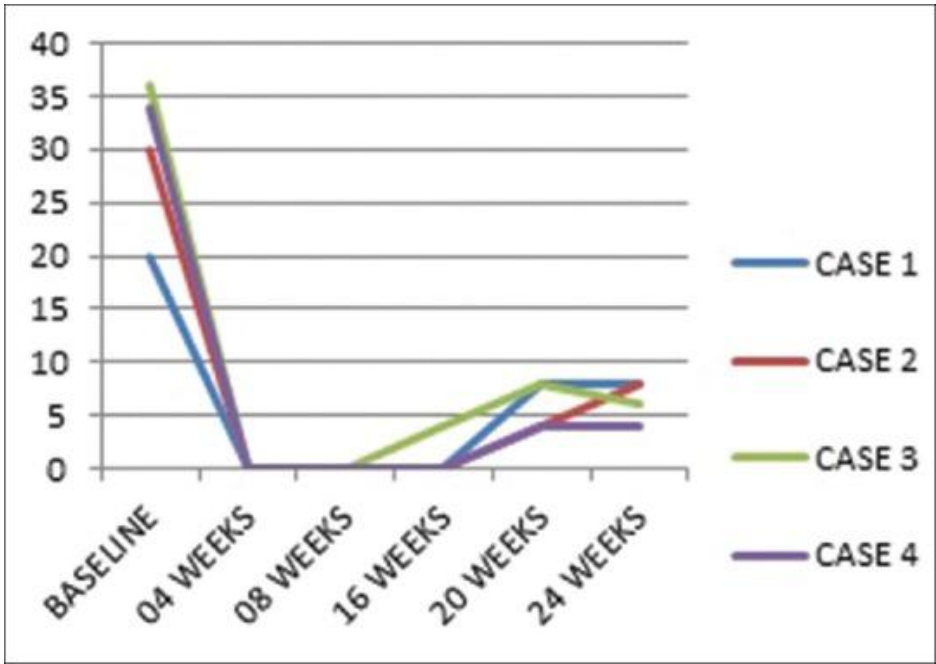
Table 4

Case number	DLQI					
	Baseline (pre-omalizumab)	4 weeks	8 weeks	16 weeks	20 weeks	24 weeks
1	20	0	0	0	6	6
2	21	0	0	0	6	8
3	24	0	0	2	8	6
4	24	0	0	0	4	4

DLQI: Dermatology Life Quality Index

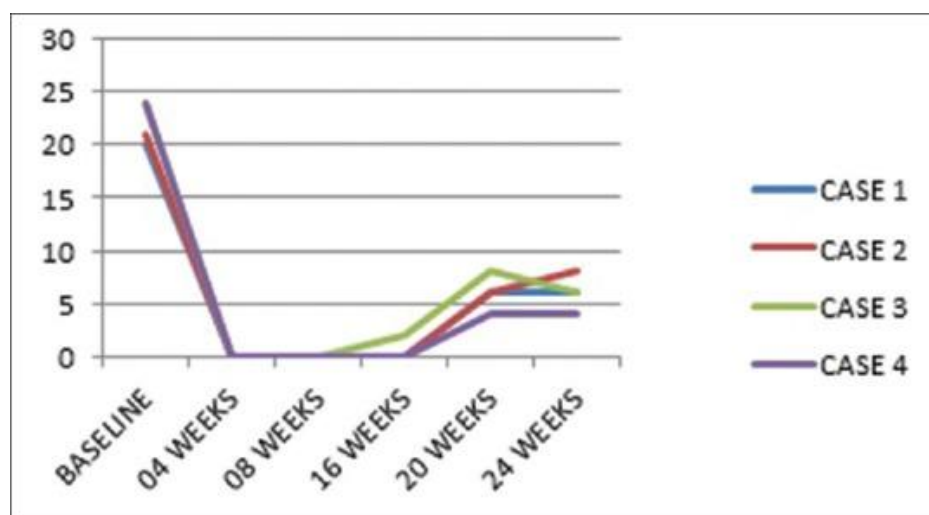
Dermatology Life Quality Index over 24 weeks follow-up period

Figure 1



Graphical description of Urticaria Activity Score 7 over the 24-week period

Figure 2



Graphical description of Dermatology Life Quality Index over the 24-week period

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