Role of Omalizumab in Refractory Chronic Spontaneous Urticaria: A Single Referral Center Experience

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Abstract

Background: Multiple evidence have shown that omalizumab, a subcutaneous (SC) anti-IgE monoclonal antibody, is highly effective for the treatment of chronic spontaneous urticaria (CSU). Objective: The objective is to evaluate the safety and efficacy of omalizumab administered 300 mg SC 1st month followed by 150 mg every month for another 5 months in cases of refractory CSU in a routine clinical setting. Materials and Methods: This was open-label, prospective, pilot study to know the efficacy and safety profile of omalizumab administered 300 mg SC first 1st month followed by 150 mg every month for another five 5 months in refractory CSU. The study was conducted at tertiary center in routine clinical setting. The primary efficacy evaluation was a change in Urticaria Activity Score-7 (UAS-7) and Urticaria Control Test (UCT) from baseline. Results: A total of 13 patients (7 females and 6 males) were enrolled in the study with the mean age of 35 years, having CSU from the mean duration of 3.15 years. Mean UAS-7 of patients decreased from 31.62 at baseline to 6.85 after the first dose of omalizumab treatment. This further reduced to 2.31 after 6 months ($P = 0.001$). Mean UCT increased from 4.46 at baseline to 13.92 after 1 month and further increased to 14.85 after 6 months ($P = 0.001$). A total of 11 patients (84.6%) achieved complete remission. Conclusion: Injection omalizumab is safe and highly effective therapy for refractory CSU in the routine clinical setting. It can be made cost effective without compromising the efficacy in resource-poor country of Indian subcontinent if barring first dose other can be halved of recommended dose. However, small number of patients, uncontrolled study and lack of long-term follow-up data are the limitations of the study.

Keywords: Chronic spontaneous urticaria, omalizumab, urticaria activity score 7, urticaria control test

Introduction

As per the current guideline, updated by the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA2 LEN/EDF/WAO), chronic urticaria (CU) are two types; chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU). CSU is a distinct entity defined as the spontaneous appearance of wheals, angioedema, or both of ≥6-week duration due to known or unknown causes. It does not include causes of CINDU which are symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria, and aquagenic urticaria.[1]

The pathogenesis of CU is still complex and not yet fully understood. However, central to our current understanding, now urticaria is considered to be mast-cell-driven disease. Histamine and other mediators, such as platelet-activating factor and cytokines released from activated mast cells, result in sensory nerve activation, vasodilatation, and plasma extravasation as well as cell recruitment to urticarial lesions.[1,2]

EAACI/GA2 LEN/EDF/WAO recommend licensed doses of modern, second-generation, nonsedating H1-antihistamines as the first-line treatment; if symptoms persist even after 2 weeks, dose escalation (up to four times) is advised. It has been studied that despite the increased dose of antihistaminics, 45% of CU patients remain unresponsive to treatment. In such patients whose CU is inadequately controlled by licensed or
higher doses of H1-antihistamines, guidelines recommend the third-line addition of omalizumab, ciclosporin, or the leukotriene receptor antagonist montelukast to existing H1-antihistamine therapy.[1]

Now, there are many evidences which include case reports and case series as well as double-blind placebo-controlled studies which establish omalizumab to be very effective in the treatment for refractory CSU.[3-11] Reports of omalizumab in refractory CSU are very limited from Indian subcontinent. This study aims to find out role of omalizumab in refractory CSU in routine clinical setting.

**Materials and Methods**

This was an open-label, prospective, pilot study to know the efficacy and safety profile of omalizumab administered 300 mg subcutaneous (SC) 1st month followed by 150 mg every month for another 5 months in the routine clinical setting. It was also decided that if urticaria is not controlled even a month later from baseline, or breakthrough lesions are appearing after initial control, subsequent dose will remain 300 mg for rest of the period. Written consent from patients and approval from the ethics committee of Institution taken before induction into the study. A total of 13 patients meeting the definition of refractory CSU were enrolled in the study. Term 'refractory urticaria' was based on study by Zuberbier et al.[1] while assessment tools to judge severity of urticaria-like urticaria activity score (UAS-7) and urticaria control test (UCT) were based upon study by Mlynek a et al.[12] and Weller K et al.[13] respectively. For this study “Refractory CSU” was defined as having wheals or wheal with angioedema without any known external triggers lasting from >6 weeks, not responding to even four times dose of standard oral nonsedative antihistaminics for a week, a history of the use of systemic glucocorticoid or cyclosporine or methotrexate either once or at multiple occasion for >30-day duration and 7-day UAS-7 higher than 28, and UCT<11. The study was conducted at a tertiary center in the routine clinical setting from April 2015 to March 2016. The primary efficacy evaluation was a change in UAS-7 and UCT from baseline. At the baseline complete blood count, urine analysis, liver function test with enzymes, blood sugar, blood urea, serum creatinine, chest X-ray, autologous serum skin testing (ASST), and anti-thyroid peroxidase antibody (TPO Ab) tests were conducted. History of any known diet or drug allergy or any comorbidity were noted. It was decided that oral antihistaminic what patients were on will be continued daily once or will be added if required by the patients. When patients do not have wheal or itch, they will be advised to stop the oral antihistamines.

The UAS-7 is a prospective composite scoring system based on the patient’s diary using numeric severity ratings from 0 to 3 (0 – none; 1 – mild; 2 – moderate; 3 – intense) for the number of wheals per 24 h and the intensity of pruritus. The total daily score (sum of the wheal and pruritus scores) could, therefore, assume any value between 0 and 6 which is summarized over week for UAS-7 (maximum score is 42). Any score >28 is considered severe CSU.[1,12]

UCT was based on the study of Weller et al. This test measures retrospective urticaria control of last 4 weeks based on four sets of questions, namely, on physical symptoms (pruritus and wheals), quality of life, treatment, and overall control. Each answer is scored from 0 to 4 (very much – 0, much – 1, somewhat – 2, a little – 3, not at all – 4). Score of 16 means urticaria is fully controlled while <11 is not under control.[1,13] These patients were followed every month and results were recorded in designed pro forma. Even after, 6th doses of omalizumab patients were followed for another 16 weeks for any symptoms or adverse effects. Statistical analysis was done by IBM SPSS Statistics for Windows, Version 24.0. NY, US. Wilcoxon signed-rank test was done to know the statistical outcome. P < 0.05 was considered statistically significant.

**Results**

A total of 13 patients (7 females and 6 males) were enrolled in the study with the mean age of 35 years standard deviation (SD) (9.60), having CSU from mean duration of 3.15 years SD (1.34). Details of clinical profile are illustrated in Table 1. Three patients had prior comorbidities, while n = 5 (38.4%) and n = 1 (7.65) had ASST and anti-TPO Ab positivity, respectively. Details of score of UAS-7 and UCT at baseline, after a month, and after 6 months are illustrated in Table 2. Graphical representation of same is well depicted in the Graphs 1 and 2. Differences between the mean of UAS-7 and UCT at baseline, after 1 month, and after 6 months were statistically significant (P < 0.005). It is tabulated in Table 3. No patient had a definite history of any food allergy. Patients having serial no. 1 and 8 continued to receive antihistamines daily even after six doses of omalizumab of 300 mg monthly. At no point of time, these two were of oral antihistamines. Serial no. 3 patient, a 47-year-old lady who was ASST and anti-TPO Ab positive required an extended period of oral cetirizine 10 mg OD, so her remaining dosages of omalizumab were increased to 300 mg. While resting other patients did not require to take antihistamines after a period varying between 7 and 26 days. This is illustrated in Table 1. During the
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Table 1: Clinical profile of patients of chronic spontaneous urticaria. Also depicts number of days, since antihistamines were continued from baseline

| Number | Age | Sex | Duration in years | Past treatment | Comorbidity | ASST | Anti-TPO ab | Stop AH after (days) |
|--------|-----|-----|-------------------|----------------|-------------|------|-------------|----------------------|
| 1      | 45  | Male| 7                 | AH, CS, Cys, ASS | Negative    | Negative | Could not stop |
| 2      | 25  | Female| 3                 | AH, CS, Cysp    | Positive    | Negative | 22          |
| 3      | 47  | Female| 2                 | AH, CS         | Positive    | Positive | 36          |
| 4      | 32  | Female| 4                 | AH, CS, Cys     | Negative    | Negative | 9           |
| 5      | 43  | Male | 2                 | AH, CS, MTX    | Negative    | Negative | 7           |
| 6      | 25  | Male | 3                 | AH, CS, Cys    | Positive    | Negative | 24          |
| 7      | 44  | Male | 3                 | AH, CS, Cysp   | Negative    | Negative | 7           |
| 8      | 38  | Female| 2                | AH, CS, Cysp   | Negative    | Negative | Could not stop |
| 9      | 46  | Male | 3                 | AH, CS, MTX   | Positive    | Negative | 8           |
| 10     | 32  | Female| 4                 | AH, CS, Cys     | Negative    | Negative | 7           |
| 11     | 35  | Male | 3                 | AH, CS, Mtx    | Negative    | Negative | 15          |
| 12     | 23  | Female| 2                | AH, CS, Cys    | Positive    | Negative | 26          |
| 13     | 20  | Female| 3                | AH, CS, Cysp   | Negative    | Negative | 10          |

AH: Antihistaminics, CS: Corticosteroid, Cys: Cyclosporine, Mtx: Methotrexate, ASS: Autologous serum, ASST: Autologous serum skin testing, Anti-TPO ab: Anti-thyroperoxidase ab, Htn: Hypertension

Table 2: Urticaria Activity Score-7 and Urticaria Control Test score at baseline, after 1 month, after 6 months, and after 16 weeks of follow-up

| Number | UAS7 baseline | UCT baseline | UAS7 after 1 month | UCT after 1 month | UAS7 after 6 months | UCT after 6 months | UAS7 after 16 weeks of follow-up | UCT after 16 weeks of follow-up |
|--------|---------------|--------------|--------------------|-------------------|---------------------|--------------------|-------------------------------|-------------------------------|
| 1      | 32            | 4            | 17                 | 7                 | 14                  | 9                  | 15                           | 8                             |
| 2      | 36            | 3            | 2                  | 16                 | 0                   | 16                 | 0                            | 16                            |
| 3      | 28            | 4            | 14                 | 14                 | 4                   | 16                 | 6                            | 12                            |
| 4      | 32            | 4            | 3                  | 16                 | 0                   | 16                 | 0                            | 16                            |
| 5      | 30            | 3            | 2                  | 16                 | 0                   | 16                 | 0                            | 16                            |
| 6      | 31            | 5            | 2                  | 16                 | 0                   | 16                 | 0                            | 16                            |
| 7      | 33            | 7            | 3                  | 16                 | 0                   | 16                 | 0                            | 16                            |
| 8      | 34            | 3            | 20                 | 6                  | 12                  | 8                  | 14                           | 6                             |
| 9      | 34            | 6            | 2                  | 16                 | 0                   | 16                 | 0                            | 16                            |
| 10     | 30            | 4            | 3                  | 16                 | 0                   | 16                 | 0                            | 16                            |
| 11     | 32            | 5            | 10                 | 12                 | 0                   | 16                 | 0                            | 16                            |
| 12     | 28            | 6            | 3                  | 16                 | 0                   | 16                 | 0                            | 16                            |
| 13     | 31            | 4            | 8                  | 14                 | 0                   | 16                 | 0                            | 16                            |

UAS7: Urticaria Activity Score-7, UCT: Urticaria Control Test

Graph 2: Urticaria Control Test score from baseline to 1 month, 6 months, and after 16 weeks of follow-up

Discussion

The available data indicate that urticaria has a detrimental effect on the quality of life. O’Donnell et al.\cite{14} showed that health status scores in patients with CSU are comparable to those reported by patients with coronary artery disease. Omalizumab is initially licensed for the treatment of allergic asthma way back in the year 2003. It has huge safety and efficacy data in bronchial asthma. Now, after going through different phases of trials, it has received approval from the European Medicines Agency and the US Food and Drug Administration for the treatment of CSU in the year 2014.\cite{15}

Omalizumab is a humanized, monoclonal, anti-IgE antibody comprising a human IgG framework onto which are incorporated the complementarity-determining regions from a murine anti-IgE antibody.\cite{16} Omalizumab binds to free IgE in the blood and interstitial space, forming biologically inactive

follow-up period, a 47-year-old lady developed intermittent mild urticaria which was controlled with oral cetirizine 10 mg once daily. Only one lady developed upper respiratory tract infection.
IgE complexes that are unable to bind to FcεRI on the surface of mast cells and basophils,[16,18,19] thereby reducing trigger to mast cell and basophil degranulation and the subsequent inflammatory cascade. By forming inactive complexes with IgE, omalizumab can also indirectly bind and sequester free allergens and possibly autoallergens such as thyroperoxidase and double-stranded DNA, which can bind to the sequestered IgE.[16] There is also an important consequence of free IgE sequestration by omalizumab, which is the downregulation of FcεRI on the surface of mast cells and basophils, and a subsequently reduced sensitivity and/or responsiveness of these cells to allergens or activating autoantibodies.[16,18,19]

In our study, a total of 11 patients (84.6%) achieved complete remission which is statistically significant ($P < 0.005$). These patients did not require taking any antihistaminics even after 16 weeks of follow-up period. Only one lady of all these required a short course of oral antihistamine, but she continues to be asymptomatic now. Two patients who continue to get symptoms of CSU are well controlled with daily single dose of oral antihistaminics. In another retrospective study of 21 patients in the routine clinical setting of CSU, 83% achieved complete remission which is similar to our result.[20] The reduction in UAS-7 and UCT was quite significant within a week of omalizumab therapy. A total of 9 patients (69.2%) had immediate relief from urticaria which persisted even in follow-up period.

In a similar study, 12 patients with treatment-resistant CSU exceptionally responded to omalizumab almost at the 1st week after the beginning of the first doses. UAS and total CU Quality of Life Questionnaires (CU-Q2oL) scores displayed significant improvements at the end of the 1st month in all 14 patients ($P < 0.000$ for both). These response levels persisted at the 6th-month control.[6] CU-Q2oL has been specifically developed by Baiardini et al. for use in patients with CU and encompasses the physical, emotional, social, and practical domains that characterize this condition. It consists of 23 items categorized under the following scales: pruritus, swelling, impact on life activities, sleep problems, limits, and looks.[21] Questionnaires based on CU-Q2oL were found difficult by our patients to follow before induction into the study. Therefore, these parameters could not be applied in our study.

Studies of omalizumab on CSU from India are very limited. Table 4 describes the three Indian studies[22–24] done on omalizumab in CSU.

Omalizumab being a subcutaneously administered injection is easy to administer in the routine clinical setting. Even though anaphylaxis is very remote adverse effect,[13] dermatologist shall keep anaphylactic tray ready while administering this. Only one lady, an obese patient developed upper respiratory tract infection following omalizumab therapy which was

| Score | Mean with SD at baseline | Mean with SD after 1 month | Mean with SD after 6 months | Mean with SD after 16 weeks of follow-up | $P$ (two-tailed) difference between baseline to 1 month | $P$ (two-tailed) difference between baseline to 6 months |
|-------|--------------------------|----------------------------|-----------------------------|------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|
| UAS-7 | 31.62 (2.32)             | 6.85 (6.40)                | 2.31 (4.88)                 | 2.69 (5.40)                             | 0.001                                                  | 0.001                                                  |
| UCT   | 4.46 (1.26)              | 13.92 (3.52)               | 14.85 (2.82)                | 14.31 (3.44)                            | 0.001                                                  | 0.001                                                  |

UAS-7: Urticaria Activity Score-7, UCT: Urticaria Control Test, SD: Standard deviation

**Table 4: Indian studies on injection omalizumab in chronic spontaneous urticaria**

| Study by          | Brief of patient                                                                 | Dose and duration of omalizumab | Outcome of the treatment                                                                 | Adverse effects             | Follow-up                  |
|-------------------|----------------------------------------------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------|-----------------------------|---------------------------|
| Godse, 2008[22]   | A single case study of a 45-old-year female who presented with severe CU for 10 years not responding to antihistaminics, oral steroids, and oral cyclosporine | 300 mg SC 4 weekly for 2 months | 90% improvement in the symptom after first dose and effect lasted for 4 weeks           | Not described              | Not described             |
| Godse, 2011[23]   | Study of five patients who had severe urticaria that required multiple antihistaminics, steroids, or dapsone to control symptoms and in spite of therapy, they had severe symptoms | Dose was based on antibody E level like asthma (300 mg twice monthly to once monthly) for four months | At the end of 4 months, two patients were free from symptoms and the other three required only antihistaminics to control their symptoms | two patients in the form of headache and fatigue | Not described             |
| Subramaniyan and Chopra, 2016[24] | Study of four patients of CSU whose disease was not controlled with four times the licensed dose of tablet fexofenadine 180 mg. Previously, they have been prescribed oral prednisolone and in two cases oral cyclosporine along with oral antihistamines | Single dose of omalizumab 300 mg | Significant decline in UAS7 and DLQI in 7-10 days | Not described | One relapsed after 16 weeks and three after 20 weeks |

CSU: Chronic spontaneous urticarial, CU: Chronic urticarial, UAS7: Urticaria Activity Score-7
managed by a course of oral antibiotics. This is mentioned as common adverse effect of omalizumab.\[7,15\]

Recommended dose of omalizumab is 300 mg SC monthly for 6 months.\[1,7\] We have tried a new regimen of omalizumab when the first dose is high, i.e., 300 mg followed by 150 mg every month for 5 months considering our limited resource. This drug is very promising in the management of CSU. This regimen will cut the cost considerably and benefit the patients in the long run without compromising the efficacy. Less number of patients, uncontrolled study, and only 16-week follow-up period post-6\(^{th}\) dose are few limitations of this study. It requires large number of such patients with randomized, double-blind, placebo-controlled trial, and long-term follow-up data to convincingly prove that this drug is very effective in above dose regimen.

**Conclusion**

Omalizumab is a new armamentarium in the arm of dermatologist for cases of CSU which are difficult to treat or where the quality of life is severely compromised. This drug is very effective and safe to use in the routine clinical setting. It can be made cost effective without compromising the efficacy in subset of patients by administering the half of recommended dosage from second month onward. However, it requires large, randomised, double blinded study to prove.

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**Conflicts of interest**

There are no conflicts of interest.

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