SciMedCentral

Journal of Autoimmunity & Research

Case Report

Omalizumab Therapy for Chronic Urticaria in the Real-Life Clinical Practice Setting: The Milanese Experience

Laura Colli[1]*, Silvia Ferrucci[1], and Paolo D. Pigatto[2]

[1]*Operative Unit of Dermatology, IRCCS Foundation Ca 'Granda-Major Hospital Policlinico, Italy*

[2]*Department of Biomedical, University of Milan, Italy*

***Corresponding author**

Laura Colli, Operative Unit of Dermatology, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy, Tel: 39-02-55034717; Fax: 39-02-55034734; E-mail: laura.colli@unimi.it

Submitted: 07 August 2017

Accepted: 24 August 2017

Published: 26 August 2017

ISSN: 2573-1173

OPEN ACCESS

Keywords

• Chronic urticaria; Omalizumab; Management; Retreatment; UAS7

Abstract

Background: Chronic urticaria (CU) is a debilitating disease that sometimes is resistant to standard therapies. Omalizumab is a subcutaneous anti-IgE monoclonal antibody highly effective for the treatment of chronic urticaria. Our aim was to investigate the effectiveness of omalizumab and its adverse effects in a real-life clinical practice setting.

Materials and methods: We conducted a retrospective analysis of the data of 77 patients treated with 300 mg/month omalizumab, we evaluated the efficacy of the treatment and retreatment calculating the weekly urticaria activity score (UAS7).

Results: Seventy-seven patients received omalizumab for CU unresponsive to anti H1-antihistamines and to other medications: 54 with chronic spontaneous urticaria (CSU) alone, 3 with chronic inducible urticaria (CIndU) alone, and 20 with CSU associated with CIndU. At the end of the first month of therapy 6.7% achieved complete remission, and the complete response arose at 37.7% at the end of the first cycle of the therapy, and 42.6% never achieved complete remission but showed a marked improvement. About one half of the treated patients had a relapse after a mean of 10.6 weeks and 29 had to be re-treated. We observed few mild adverse events during the treatment with omalizumab, namely headache and arthralgya and myalgia.

Conclusion: Omalizumab 300 mg was effective in difficult to treat patients with CU with rapid onset of action, it induced a long lasting positive response and maintained remission. Omalizumab was well tolerated inducing mild and sporadic side effects. Omalizumab can be the preferred third-line therapy in patients with unresponsive CU.

ABBREVIATIONS

CU: Chronic Urticaria; CSU: Chronic Spontaneous Urticaria; Cindu: Chronic Inducible Urticaria; UAS: Urticaria Activity Score; UAS7: Weekly Urticaria Activity Score; ASST: Autologous Serum Skin Test; APST: Autologous Palsma Skin Test; NSAID: Non Steroidal Anti-Inflammatory Drug

INTRODUCTION

Chronic urticaria (CU), which includes chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), is characterized by the presence of recurrent itching, wheals and/or angioedema that lasts for more than 6 weeks [1]. The current guidelines of the European Academy of Allergy and Clinical Immunology and Global Allergy and Asthma European Network and the World Allergy Association committees suggest a therapeutic ladder to approach the management of CSU: the first step is the use of a standard dose of H1-antihistamines; the second step is to increase fourfold the dose of these drugs; the third and last step is to treat antihistamine-resistant urticaria with one drug among cyclosporine A, omalizumab or montelukast as an add-on therapy [2]. The aim is to reach the complete control of symptoms. Omalizumab is an effective and safe treatment for difficult-to-treat CU and the existing literature suggests a dosage of 300 mg every 4 weeks as a preferred therapy [3]. In Italy omalizumab can be administered only after filling in an institutional treatment plan that requires that the CU patient is ≥ 12 years of age, shows an Urticaria Activity Score (UAS) > 3 and/or a weekly Urticaria Activity Score (UAS7) > 16 defining him/her as a non-responder to H1-antihistamines. The treatment plan includes a first therapeutic cycle of 24 weeks, than an observational period of 8 weeks and a possible second cycle of treatment of 20 more weeks if the recurred disease could not be controlled with concomitant H1-antihistamines.

MATERIALS AND METHODS

This was a retrospective, real-life study with patients with severe CU treated with omalizumab at two university hospitals in Milan from September 2015 to June 2017. The included patients had a history of urticaria longer than 6 weeks and did not respond to the increase of H1-antihistamines. Age, sex, previous and current therapies, laboratory and clinical findings were recorded in a database (Table 1). Omalizumab was administered subcutaneously in doses of 300 mg every 4 weeks. The response

Table 1: Clinical parameters of 77 urticaria patients treated with omalizumab for CU.

Characteristics	Patients (n=77)
Gender (female %)	46 (60%)
Age (yr)	46 ± 15
Duration of disease (months)	76,2 ± 98,4
Other therapies than H1-antihistamines	
Short course corticosteroids	29 (37%)
Montelukast	20 (26%)
Cyclosporine	6 (8%)
Others (azathioprine or dapsone)	7 (9%)
Diagnostic group	
CSU	54 (70%)
CIndU	3 (4%)
CSU and CIndU	20 (26%)
CIndU Subtype	
Delayed pressure urticaria	7 (30%)
Dermographic urticaria	5 (22%)
Cholinergic urticaria	5 (22%)
Cold urticaria	5 (22%)
Aquagenic urticaria	1 (4%)

Abbreviations: CU: Chronic Urticaria; CSU: Chronic Spontaneous Urticaria; CIndU: Chronic Inducible Urticaria

to treatment was recorded using the UAS7 score. According to the response to omalizumab the patients were grouped as urticaria-free patients (UAS7 = 0; complete responders), patients with a well-controlled disease (UAS7 = 1-6; partial complete responders), patients with mild urticaria (UAS7 = 7-15; partial responders), patients with moderate urticaria (UAS7 = 16-27; non-responders), and patients with severe urticaria (UAS7 = 28-42; non-responders as well)[4].

RESULTS AND DISCUSSION

We recruited 77 patients (60% females) aged from 15 to 82 years (mean 46 ± 15) with few comorbidities. The mean duration of urticaria prior to omalizumab treatment was 76 months (range 6 to 540 months); urticaria was lasting more than 1 year in 94% of our patients and more than 5 years in 45% of our sample. Fifty-four (70%) patients had CSU alone and the remainders had signs of CIndU alone (3/77) or associated to CSU (30% delayed pressure, 22% dermographic, 22% cholinergic, 22% cold, 4% aquagenic urticaria). Autoimmunity was investigated by the presence of positivity of autologous serum skin test (ASST), autologous plasma skin test (APST) and/or antithyroid antibodies: 10% of patients had presence of antithyroid antibodies, and 22/77 had positivity in ASST and/or APST. We investigated the history of allergy or atopy and the 16% of our patients had an IgE level above the average.

The most frequently used antihistamine was cetirizine, but other antihistamines such as bilastine, desloratadine, hydroxyzine, ebastine, rupatadine, and fexofenadine were used. While all of our patients were in treatment with high dose antihistamines, 29 (37%) had previously received short courses of systemic glucocorticoids (prednisone or betametasone) and 33 (43%) were treated with other immune modulating agents: montelukast (26%), cyclosporine A (8%), and others such as azathioprine or dapsone (9%). All of them were unresponsive to those long course therapies.

All the patients received omalizumab in a subcutaneous dose of 300 mg/month. The treatment period ranged from 2 to 13 months and the responses are summarized in Table 2. We observed that at the end of the first month of therapy 35/77 patients showed a positive response: 5 (6.7%) were complete responders and 30 (40%) partial complete responders. At the end of the first cycle CU subsided in 49/77 patients: 23 (37.7%) patients showed a complete response and 26 (42.6%) a partial complete response. Only 2 patients discontinued the treatment before the end of the first cycle for personal issues. Complete failure of the treatment was observed in only 2 patients. We followed up the patients after the first cycle, and 33/77 had a relapse of CU after a mean of 10.6 weeks (range 4-50; mode 6). Four of them achieved a satisfactory symptomatic response with H1-antihistamines alone; 29 had to be re-treated with omalizumab because remained refractory to H1-antihistamines. The response rate at the end of the first month of the second cycle showed 10.3% of complete responders and 62.0% of partial complete responders. At the end of the second cycle 71.5% had a complete or partial complete response.

We observed only two kinds of adverse events related to omalizumab: 5 patients reported mild headache that arose right after the administration of omalizumab and lasted for 3 to 4 days; 3 patients reported arthralgia and myalgia, 2 patients had mild and 1 severe symptoms. All the adverse events cleared with the administration of NSAIDs.

This was an observational real-life study limited by the small number of patients and the variable duration of the treatments. The study was carried out to assess the efficacy of omalizumab in patients with severe CU, non-responders to other therapies and requiring short course systemic steroids to control flare ups. We observed a high efficacy of omalizumab in the vast majority of patients: even one administration was therapeutic in some of our patients but we observed that omalizumab was most effective if used for a prolonged period. The proportion of patients free of hives and pruritus was greater and greater as the number of doses raised. The positive response was followed by a clear decrease in the use of antihistamines and corticosteroids. Despite this remarkable improvement in urticarial symptoms, our complete remission rates were lower than the ones in other retrospective real-life studies [5,6]. This study included patients with CSU with or without autoimmune features and patients with CSU and associated CIndU or CIndU alone. The response rates of the first group (Table 3) were comparable to the overall response rates due to the preponderant number of patients belonging to this group. Conversely only the response rates of the first cycle of therapy in the CIndU group (Table 4) followed the trend of the other group; that was due to the scarceness of patients that reached the second cycle of therapy and the statistics measurements proved to be non significant. Despite the urticarial phenotype we observed an overall high rate of

Table 2: Response of chronic urticaria to therapy with omalizumab.

UAS7	First cycle	End of I month	End of II month	End of III month	End of IV month	End of V month	Second cycle	End of I month	End of II month	End of III month	End of IV month
≥28		12.0%	5.5%	0%	0%	3.3%		3.4%	0%	4.8%	0%
16-27		16.0%	9.6%	13.2%	9.2%	9.8%		10.3%	8.3%	4.8%	18.8%
7-15		25.3%	26.0%	20.6%	18.5%	6.6%		13.8%	16.7%	9.5%	12.5%
1-6		40.0%	35.6%	41.2%	41.5%	42.6%		62.0%	41.7%	47.6%	25.0%
0		6.7%	23.3%	25.0%	30.8%	37.7%		10.3%	33.3%	33.3%	43.8%

Abbreviations: UAS7: weekly Urticaria Activity Score

Table 3: Response of patients with CSU alone to therapy with omalizumab.

UAS7	First cycle	End of I month	End of II month	End of III month	End of IV month	End of V month	Second cycle	End of I month	End of II month	End of III month	End of IV month
≥28		14.0%	5.4%	0%	0%	0%		4.5%	0%	0%	0%
16-27		15.8%	10.7%	13.5%	6.1%	10.9%		9.1%	5.6%	6.3%	15.4%
7-15		21.1%	28.6%	19.2%	20.4%	6.5%		18.1%	22.2%	12.5%	15.4%
1-6		42.1%	33.9%	46.2%	42.9%	45.7%		54.5%	38.9%	50.0%	3.8%
0		7.0%	21.4%	21.2%	30.6%	37.0%		13.6%	33.3%	31.3%	38.5%

Abbreviations: CSU: Chronic Spontaneous Urticaria; UAS7: weekly Urticaria Activity Score

Table 4: Response of patients with CIndU alone or associated with CSU to therapy with omalizumab.

UAS7	First cycle	End of I month	End of II month	End of III month	End of IV month	End of V month	Second cycle	End of I month	End of II month	End of III month	End of IV month
≥28		5.6%	5.9%	0%	0%	13.3%		0%	0%	20.0%	0%
16-27		16.7%	5.9%	12.5%	18.8%	6.7%		14.3%	16.7%	0%	33.3%
7-15		38.9%	17.6%	25.0%	12.5%	6.7%		0%	0%	0%	0%
1-6		33.3%	41.2%	25.0%	37.5%	33.3%		85.7%	50.0%	40.0%	0%
0		5.6%	29.4%	37.5%	31.3%	40.0%		0%	33.3%	40.0%	66.7%

Abbreviations: CIndU: Chronic Inducible Urticaria; CSU: chronic Spontaneous Urticaria; UAS7: weekly Urticaria Activity Score

responsiveness and we did not notice any laboratory marker predictor of response or lack of response to omalizumab. The only parameter that showed a correlation to the improvement of urticaria severity was the D-dimer which lowered in responders with elevated baseline D-dimer [7]. Improvement in disease was independent of age, sex, disease duration and severity and previous therapies [8]. According to previous studies, few of our patients showed a rapid symptom control within days after the beginning of treatment (fast-responders) [9] which cannot be explained by the downregulation of FcεRI receptors but could be via the removal of IgE, auto-allergen sequestration and improvement of basophils IgE receptor function [10]. Furthermore we found that the strength and the celerity of the response did not correlate with the long-term remission.

CU is characterized by spontaneous remissions and exacerbations. In our cohort the majority of patients that had a relapse of urticaria after the first cycle developed UAS7 scores similar to their baseline which accords to previous studies [11]. Less than a half of our patients remain in remission, but we do not know if it is due to a long term remission induced by omalizumab rather than spontaneous resolution. In patients that had a relapse after the first cycle, the original response to omalizumab was restored after the first or second month of re-treatment. We had not any loss of efficacy of omalizumab in our patients.

In our study we noticed a very good safety profile registering mild to moderate adverse events in few patients as shown in previous studies [12,13].

CONCLUSION

We found omalizumab to be safe and effective in patients with CU regardless their age, sex, previous medication taken, and the immune process underlying their condition. In our experience omalizumab had a rapid onset of action and was capable of controlling symptoms for long periods so much so that some patients achieved a long-standing remission. Omalizumab does not require laboratory assessment during the therapy and reduces direct costs [3], so it can become the preferred third-line therapy in patients non responsive to antihistamines.

REFERENCES

1. Maurer M, Weller K, Bindslev-Jensen C, Giménez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report. Allergy Eur J Allergy Clin Immunol. 2011; 66: 317-330.

2. Zuberbier T, Aberer W, Asero R, Brzoza Z, Canonica GW. The EAACI / GA 2 LEN / EDF / WAO Guideline for the definition, classification,

diagnosis, and management of urticaria: the 2013 revision and update. Allergy. 2014; 69: 868-887.

3. Tonacci A, Billeci L, Pioggia G, Navarra M, Gangemi S. Omalizumab for the Treatment of Chronic Idiopathic Urticaria : Systematic Review of the Literature. Pharmacotherapy. 2017; 37: 464-480.

4. Stull DE, McBride D, Gimenez-Arnau A, Grattan C, Khalil S, Balp MM. Categorical Health States In Chronic Spontaneous Urticaria (Csu) Based On The Weekly Urticaria Activity Score (Uas7): Are They Distinct, Discriminative, And Reproducible?. Value Health. 2014; 17: 611.

5. Sussman G, Hébert J, Barron C, Bian J, Caron-Guay RM, Laflamme S, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. Ann Allergy Asthma Immunol. 2014; 112: 170-174.

6. Rottem M, Segal R, Kivity S, Shamshines L, Graif Y, Shalit M, et al. Omalizumab therapy for chronic spontaneous urticaria: The Israeli experience. Isr Med Assoc J. 2014; 16: 487-490.

7. Asero R, Marzano V, Ferrucci S. D-Dimer Plasma Levels Parallel the Clinical Response to Omalizumab in Patients with Severe Chronic Spontaneous Urticaria. Int Arch Allergy Immunol. 2017; 40-44.

8. Casale TB, Bernstein JA, Maurer M, Saini SS, Trzaskoma B, Chen H, et al. Similar Efficacy with Omalizumab in Chronic Idiopathic/Spontaneous Urticaria Despite Different Background Therapy. J Allergy Clin Immunol Pract. 2015; 3: 743-750.

9. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: A retrospective clinical analysis. J Dermatol Sci. 2014; 73: 57-62.

10. Kaplan AP, Gimenez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. Allergy Eur J Allergy Clin Immunol. 2017; 72: 519-533.

11. Maurer M, Rosén K, Husieh H-J, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria: A critical appraisal. N Engl J Med. 2013; 368: 924-935.

12. Saini SS, Bindslev-Jensen C, Maurer M, Grob J-J, Bülbül Baskan E, Bradley MS, et al. Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria Who Remain Symptomatic on H1 Antihistamines: A Randomized, Placebo-Controlled Study. J Invest Dermatol. 2015; 135: 67-75.

13. Michihiro H, Hae-Sim P, Atsuyuki I, Young-Min Y, Tae-Bum K, Akiko Y, et al. Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria. J Dermatol Sci. 2017; 87: 70-78.

Cite this article

Colli L, Ferrucci S, Pigatto PD (2017) Omalizumab Therapy for Chronic Urticaria in the Real-Life Clinical Practice Setting: The Milanese Experience. J Autoimmun Res 4(3): 1027.