ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.413
Asthma Allergy Immunol 2019;17:41-46

RESEARCH ARTICLE

Received: 13/02/2018 • Accepted: 18/04/2018

Efficacy of Omalizumab in Treatment-Resistant Chronic Spontaneous Urticaria

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ABSTRACT

Objective: Chronic spontaneous urticaria is a disorder characterized by spontaneous development of pruritic erythematous plaques, angioedema or both. Omalizumab is a recombinant monoclonal antibody that selectively binds to IgE and inhibits its binding to FceRI receptors on mast cells and basophils. We sought to retrospectively assess the efficacy of Omalizumab, the adverse effects due to treatment, and the disease-free duration after treatment in treatment-resistant chronic spontaneous urticaria cases.

Materials and Methods: The treatment responses of 24 chronic spontaneous urticaria cases treated with Omalizumab at our clinic were retrospectively evaluated.

Results: The mean age of the patients was 44 years and the mean duration of disease was 7.2 years. The most common concomitant systemic disease was thyroid disease (29%). The duration of treatment ranged from 4 to 36 months, and total treatment doses from 5 to 28 doses. The treatment of 15 patients was still going on and the mean duration of treatment was 24.4 months. Disease control could not be achieved in three patients but the mean dose of disease control was 3.2 in the other patients. The treatment response was partial in 29% (n=7) and complete in 71% (n=17) of the patients. Side effects (erythema or urticarial plaque at the injection area, headache, dizziness, myalgia, arthralgia) were detected in eight patients. No recurrence was detected in five patients with a mean follow-up duration of 12 months after the treatment. The mean duration until recurrence was 7.7 months after the treatment in five patients who had recurrence.

Conclusion: Omalizumab is a good treatment option, thanks to its efficacy and safety, in chronic spontaneous urticaria patients who do not respond to H1-antihistamines.

Key words: Urticaria, therapeutics, histamine antagonists, Omalizumab, safety

INTRODUCTION

Chronic spontaneous urticaria (CSU); is a disorder characterized by spontaneous development of pruritic erythematous plaques, angioedema, or both; relapsing without a certain reason and persisting for 6 weeks or more (1). The pathogenesis of CSU lesions resembles allergen-mediated, delayed-type skin reactions where mast cells and basophils play role by FcεRI activation (2).

Nonsedative H1-antihistamines are the first line therapy and it is recommended to increase the dose up to four-fold in case there is no response. If the symptoms persist after a treatment duration of one-four weeks, Omalizumab, Cyclosporin A or Montelukast can be added to the treatment (3). Recently, many studies have been reported the efficacy of treatment with Omalizumab in CSU patients resistant to conventional treatment.

Omalizumab, a humanized IgG type monoclonal antibody that recognizes the Fc portion of IgE, has been used in standard treatment-resistant allergic asthma or atopic dermatitis (4). The use of Omalizumab in CSU patients was approved in 2014 and it became the first drug to be approved for patients resistant to H1-antihistamines (5, 6). By blocking the binding of IgE to the FceRI receptor on mast cells and basophils, Omalizumab decreases the expression of receptor and the release of inflammatory mediators (7).

We sought to retrospectively investigate the efficacy, treatment-related adverse effects and disease-free duration after treatment in treatment-resistant CSU patients in our study.

MATERIALS and METHODS

The Institutional Ethics Committee of our research hospital approved the project (E-16-968) and informed consent was obtained from the subjects. The treatment responses of 24 patients with CSU that received Omalizumab treatment at our department between July 2013 and June 2016 were evaluated retrospectively. Demographic findings of the patients such as duration of treatment, history of angioedema, history of concomitant systemic diseases, and history of treatment for CSU were recorded. The levels of the markers of thyroid autoimmunity [anti-thyroglobulin (antiTG) and anti-thyroidperoxidase (antiTPO)] were obtained from the records.

The dosages and intervals of Omalizumab treatment, duration of treatment, dose of disease control (the first dose after which the patient became asymptomatic), side effects of treatment, response to treatment, the time period until recurrence, and follow-up data were investigated. Complete response to treatment was accepted as the disappearance of urticarial plaques and angioedema attacks.

The initial doses of Omalizumab had been 150 mg every two weeks or 300 mg once a month according to the severity of the disease. The frequency of treatment was progressively decreased by prolonging the intervals of the doses by one or two weeks in patients who responded to the treatment.

RESULTS

In total, 24 patients (22 female, 2 male) were included in our study. The patients were either under Omalizumab treatment or had completed the treatment. The mean age of the patients was 44 (range: 20-61) years and the mean disease duration was 7.2 years (range: 2 months - 40 years). Angioedema accompanied the urticaria in 13 (54%) patients. The most common concomitant systemic disease was thyroid disease (29%). Thyroid autoantibodies were investigated in 23 patients and were positive in 5 (22%) of them. In the evaluation of previous treatments; all of the patients were resistant to four-fold doses of second generation antihistaminics while there was no response to corticosteroids in eight, cyclosporine in five, and leukotriene antagonists in five patients. Autohemotherapy was performed in one patient and danazole treatment was tried in another patient, but neither was useful (Table I).

The duration of treatment ranged from 4 to 36 months, and total treatment doses from 5 to 28 doses. The treatment of 15 patients was still going on and the mean duration of treatment was 24.4 months. Disease control could not be achieved in three patients (new lesion appearance was recorded before each injection in patients number 18 and 22; and all along the treatment in patient number 24). The mean dose of disease control was 3.2 in the rest of the patients.

The response to treatment was partial in seven (29%) patients, while complete response was obtained in 17 (71%) patients. The mean duration of disease was longer in complete responders (7.1 years) than the partial responders (5.6 years).

In the evaluation of treatment side effects; erythema was observed at the injection area in one patient and an urticarial plaque in another patient. After the injection; three patients described headache, two patients myalgia, one patient arthralgia, and one patient dizziness. No side effects were recorded in 66% (n=16) of the patients.

At the endpoint of the study period, 15 patients were still under Omalizumab treatment. The treatment of patient number 6 was terminated because of a cerebrovascular occlusion attack. Patient number 5 did not come to follow-ups. There was no recurrence in five patients with a mean of 12 (5-24) months of follow-up after the treatment was stopped. The mean duration until recurrence was 7.7 (5-12) months in three patients who had recurrence in our study (Table II).

DISCUSSION

Omalizumab is a recombinant monoclonal antibody that specifically binds IgE and inhibits its binding to FceRI on the surface of mast cells and basophils (8). The decrease in the level of free IgE results in the decrease in the expression of FcεRI receptors and decrease in FcεRI+ and IgE+ cells in dermis. The clinical efficiency of Omalizumab in CSU has been considered to be related to a decrease in the number of FcεRI+ cells in the skin. Furthermore, it was recently reported that Omalizumab can also provide detachment of the IgE that was previously attached to mast cells and basophils (2).

Table I. Demographic features of the patients

Patient	Age	Gender	Duration of disease	History of angioedema	Comorbidities	Thyroid autoantibodies	Previous treatments
1	26	F*	3 years	+	depression	-	CS‡, Cyc§, autohemotherapy
2	54	F	6 years	+	depression, HT¶ hypothyroism	-	-
3	58	F	15 years	-	HT, asthma	-	-
4	39	F	7 years	+	-	-	-
5	22	F	1 years	+	asthma	-	CS
6	33	F	8 years	+	iron deficiency anemia	-	-
7	40	F	24 years	+	Hashimoto thyroiditis, MNG||||	+	CS, Cyc, LTA||.
8	39	F	15 years	-	-	+	-
9	40	M†	7 years	+	-	-	CS, Cyc, LTA, danazol
10	60	F	2 months	+	HT	-	-
11	41	F	7 years	-	asthma	not studied	LTA
12	56	F	15 years	-	HT, DM**, HF††, asthma, CRF‡‡	-	-
13	50	F	3 months	+	-	+	CS
14	61	F	6 years	+	HT	-	CS
15	40	F	1.5 years	+	hypothyroidism	+	-
16	20	F	3 months	-	-	-	CS
17	50	M	6 years	-	-	-	-
18	32	F	3 years	+	hypothyroidism, PCOS§§	-	-
19	61	F	3 years	-	-	-	Cyc
20	58	F	40 years	+	DM, HT, asthma	-	Cyc, CS, LTA
21	45	F	6 months	-	-	-	-
22	56	F	4 months	-	hypothyroidism, asthma	+	-
23	22	F	2 years	-	-	-	-
24	53	F	1 years	-	DM, asthma	-	LTA

***F:** Female, † **M:** Male, ‡ **CS:** Corticosteroid, § **Cyc:** Cyclosporine, || **LTA:** Leukotriene antagonist, ¶ **HT:** Hypertension, ****DM:** Diabetes mellitus, †† **HF:** Hearth failure, ‡‡ **CRF:** Chronic renal failure, §§ **PCOS:** Polycystic ovary syndrome, |||| **MNG:** Multinodular goiter.

Omalizumab has high efficacy and a very good adverse effect profile in antihistamine-resistant CSU (9); in addition, it has been reported that it significantly improves the urticaria activity scores and quality of life scores in CSU (10). According to the last reported EAACI/GA2LEN/EDF/WAO guidelines; Omalizumab is recommended as third line therapy, in addition to second generation H1 antihistamines in CSU (3).

The response to Omalizumab has been reported to appear in the first weeks of the treatment (7,11-13). Metz et al. (13) reported that they recorded complete symptom control in 12 of the 21 CSU patients in the first 24 hours. In our study, the symptoms disappeared in seven of the 24 patients and clinical response was recorded after the first dose in two other patients.

Many studies have been conducted to determine the optimum dose of Omalizumab in the treatment of urticaria (1,7,14,15). In their systematic review, Urgert et al. (16) reported that there is a high level of evidence for the effectiveness and safety of Omalizumab 300 mg per month for up to six months in the treatment of CSU.

In their systematic review, Carillo et al. (14) evaluated the efficacy and safety of Omalizumab in controlling symptoms of CIU/CSU. Among the different doses used in the studies Omalizumab, 300 mg had a clear benefit in the treatment of the disease. Nevertheless, the 300 mg dose of Omalizumab was more frequently associated with adverse effects (headache and upper respiratory infection).

Table II. Treatment data of the patients

Patient	Omalizumab treatment schema	Duration of treatment	Dose of disease control	Adverse effect	Treatment response	Follow-up
1	150 mg/2 weeks 150 mg/month	5 months (7 doses)	4	erythema at the injection area	complete	no recurrence (in 24 months of follow-up)
2	150 mg/2 weeks 300 mg/month 300 mg/6 weeks	31 months (26 doses)	2	-	complete	treatment was continuing
3	300 mg/month 300 mg/6 weeks	29 months (24 doses)	8	-	partial (intermediate attacks)	treatment was continuing
4	300 mg/month	5 months (6 doses)	5	myalgia	complete	recurrence (12 months later)
5	300 mg/month	4 months (5 doses)	-	myalgia	partial	lost to follow-up
6	150mg/2 weeks 300 mg/month	12 months (15 doses)	2	headache	complete	recurrence (5 months later)
7	150 mg/2 weeks 300 mg/month 300 mg/5 weeks	34 months (27 doses)	8	headache, arthralgia	partial (intermediate attacks)	treatment was continuing
8	300 mg/month	24 months (18 doses)	2	-	complete	treatment was continuing
9	300 mg/month	25 months (22 doses)	2	-	complete	treatment was continuing
10	300 mg/month 300 mg/6 weeks 300mg/8 weeks	24 months (18 doses)	3	-	complete	treatment was continuing
11	300 mg/month	24 months (22 doses)	1	-	partial (intermediate attacks)	treatment was continuing
12	300 mg/month 300 mg/5 weeks	14 months (13 doses)	1	-	complete	recurrence (6 months later)
13	300 mg/month 300 mg/6 weeks	17 months (15 doses)	1	-	complete	treatment was continuing
14	300 mg/month 300 mg/5 weeks 300 mg/6 weeks	18 months (17 doses)	4	-	complete	treatment was continuing
15	300 mg/month 300 mg/5 weeks	13 months (9 doses)	1	-	complete	no recurrence (in 12 months of follow-up)
16	300 mg/month	11 months (11 doses)	3	headache	complete	no recurrence (in 7 months of follow-up)
17	300 mg/month 300 mg/8 weeks 300 mg/3 month	19 months (15 doses)	1	-	complete	treatment was continuing
18	300 mg/month 300 mg/5 weeks 300 mg/6 weeks	19 months (18 doses)	attack before each dose	-	partial	no recurrence (in 5 months of follow-up)
19	300 mg/month 300 mg/6 weeks 300 mg/8 weeks	22 months (15 doses)	1	-	complete	treatment was continuing
20	150 mg/2 weeks 150 mg/month	36 months (28 doses)	1	-	complete	treatment was continuing (no attack in last 12 months)
21	300 mg/month 300 mg/6 weeks	20 months (14 doses)	10	-	complete	treatment was continuing
22	300 mg/month 300 mg/6 weeks 300 mg/8 weeks	19 months (15 doses)	attack before each dose	dizziness	partial	treatment was continuing
23	300 mg/month	24 months (13 doses)	4	urticarial plaque at the injection area	complete	treatment was continuing
24	300 mg/month 300 mg/2 weeks	6 months (9 doses)	-	-	partial	no attacks in 12 months of follow-up

Kaplan et al. (1) analyzed three pivotal Omalizumab trials in their study and the best results in controlling CIU/CSU symptoms were obtained with the use of 300 mg of Omalizumab. The benefits of Omalizumab treatment were evident before week four and persisted to week 24 in some patients.

In 2016, Zhao et al. (17) reported a meta-analysis of seven randomized, placebo-controlled trials, in order to evaluate the efficacy and safety of various doses of Omalizumab for the treatment of CSU. Patients were treated with 75-600 mg Omalizumab every four weeks. Omalizumab's effects were dose dependent, and rates of complete response were significantly higher in the 300 mg group. Adverse event rates were similar in the Omalizumab and placebo groups. This meta-analysis proved the efficacy and safety of Omalizumab in patients with CSU and supported the treatment of patients with 300 mg of Omalizumab every four weeks.

Pinto Gouveia et al. (15) suggested that the Omalizumab dose and administration interval could be individualized for long-term management of CSU and the dose and interval could eventually require adjustment due to disease worsening during the treatment.

The approved dose of Omalizumab in the US is 150 or 300 mg subcutaneously every four weeks whereas in Europe, the optimum benefit-risk profile is considered to be provided by 300 mg every four weeks. Moreover, patients with angioedema and those with a body weight >80 kg have been considered to require the 300 mg dose (18).

Casale et al. (19) reported that regardless of background therapy, Omalizumab 300 mg is safe and effective in reducing CIU/CSU symptoms. In our study, a complete response was obtained even with a dose of 150 mg Omalizumab in four patients who had not responded to three or more other treatment alternatives previously.

In their study in which the patients were treated with 150 or 300 mg of Omalizumab every 4 weeks, Ensina et al. (20) reported that the complete response rates were higher in those using high-dose initial treatment. In our study, a complete response was obtained in all five patients treated with an initial dose of 150 mg while only 13 (68%) of the 19 patients who were started a dose of 300 mg Omalizumab reached a complete response and the responses were partial in the rest of them.

Chaykivska et al. (21) reported an elevated titer of anti-TPO antibodies in 17.4% of the patients with CSU in their study. It is reported in the literature that some of the autoantibodies in CSU patients are in the form of IgE and that IgG-anti-TPO levels are significantly high as well in IgE-anti-TPO positive patients (11, 22). Omalizumab treatment was proposed to be effective not only by reducing the free IgE levels but also by reducing the autoantibodies in the form of IgE (22, 23). By emphasizing that none of the complete responders to Omalizumab treatment in their study were IgG-anti-TPO positive, Türk et al. (24) suggested that autoimmune markers might be helpful in predicting the treatment response and relapse. Since four (80%) of the five patients whose thyroid autoantibodies were positive responded to Omalizumab treatment completely, whereas the complete response rate was 71% in patients whose thyroid autoantibodies were negative, thyroid autoimmunity did not seem to be a predictive factor of treatment response in our study.

Since few adverse effects have been reported with Omalizumab and most of them are minor, it appears to be a safe and well-tolerated drug. Skin reactions at the injection site (pain, swelling, erythema and pruritus) and urticaria were the most common adverse reactions reported (25). Headache, sinusitis, arthralgia and upper respiratory tract infections are the other reported adverse effects (16). In their multicenter, randomized, double-blind study where they assessed the efficacy and safety of Omalizumab in moderate-to-severe CSU patients, Maurer et al. (12) reported that severe adverse effects were encountered more frequently in the group that was treated with the highest dose (300 mg) of Omalizumab. The adverse effects that were recorded in our study were erythema or urticaria at the injection site, headache, myalgia, arthralgia and dizziness. Since most of the patients reached a final dose of 300 mg and only two patients reached a maximum dose of 150 mg, we could not detect a relation between adverse effects and the Omalizumab dose.

Although the clinical studies provide very little information about the duration of relapse, it is well known that Omalizumab treatment is a symptomatic treatment and the symptoms will always relapse after the treatment is ended. In most of the patients an interval of 4-8 weeks is enough for the symptoms to reappear; however, some patients might stay asymptomatic for longer durations (13). The mean duration until recurrence was 7.7 (5-12) months in three patients who had recurrence in our study.

CONCLUSION

As the results of our study and many studies in the literature reveal, Omalizumab is a good option with its efficacy and safety in the treatment of CSU patients who are unresponsive to H1 antihistamines. Nevertheless, there is a need for well-designed studies in order to determine the most convenient patient profile for Omalizumab treatment, optimum duration of treatment, and potential long-term adverse effects.

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