Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2014;23:57-61
doi: 10.15570/actaapa.2014.14

Omalizumab in chronic urticaria: our experience and literature review

Mitja Košnik[1] ✉, Peter Kopač[1], Renato Eržen[1], Nissera Bajrović[1], Katja Adamič[1], Nika Lalek[1], Peter Korošec[1], Mihaela Zidarn[1]

Abstract

Introduction: Chronic urticaria (CU) severely affects quality of life. If symptoms are not controlled by antihistamines, patients need immunomodulatory drugs. Recent studies show a tremendous effect of omalizumab, a monoclonal antibody against human IgE in refractory CU.

Methods: We report on the use of omalizumab in four patients with CU. By reviewing medical files, we estimated the proportion of CU patients that are candidates for such treatment. We reviewed the literature to compare the dosing schedules and outcome measures used in different studies.

Results: Up to 14% of CU patients referred to a tertiary center are candidates for omalizumab. Four of our CU were patients treated with doses of 150 mg/month or less, and all responded with nearly complete remission of symptoms. In the literature, 90% of patients respond to treatment, the response being obvious in days. Half of patients were able to stop all other medications, including antihistamines. More than half of patients responded well to doses of 150 mg of omalizumab every 4 to 8 weeks. In the majority of patients, the disease relapsed after discontinuation of omalizumab.

Conclusions: Omalizumab should be offered to patients with refractory CU. The duration of treatment is not known.

Keywords: urticaria, antihistamines, omalizumab, dosing schedule, quality of life

Received: 9 August 2014 | **Returned for modification:** 17 August 2014 | **Accepted:** 1 September 2014

Introduction

Chronic urticaria (CU) is characterized by itchy or burning hives. Individual hives last 1 to 24 hours and thereafter the skin returns to its normal appearance. Hives, angioedema, or both appear on most days for at least 6 weeks. Lesions are due to histamine and other mast cell– and basophil-derived mediators. In chronic spontaneous urticaria (CSU), hives appear without an obvious trigger. In chronic inducible urticaria (CIndU) such as dermographism, delayed pressure, cold, solar, heat, and cholinergic urticaria, symptoms are induced by physical stimuli. CU severely affects quality of life (1).

According to recent guidelines, the severity of CSU should be assessed by a validated clinical scoring system called the urticaria activity score (UAS). Patients record the extent of skin lesions and intensity of pruritus on a scale between 0 and 3. Wheals are scored as 0 (no wheals), 1 (< 20 wheals / 24 h), 2 (20–50 wheals / 24 h), or 3 (> 50 wheals / 24 h or large confluent areas of wheals) and pruritus as 0 (none), 1 (mild: present but not annoying or troublesome), 2 (moderate: troublesome but does not interfere with normal daily activity or sleep), or 3 (intense: severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep). The maximum UAS is 6.

Activity of CSU is followed by the urticaria activity score over a 7-day period (UAS7) (2). The patient assesses the severity of urticaria by UAS once a day for 7 days, and the sum of daily scores is calculated. The maximum UAS7 score is 42.

In addition to avoiding triggers of wheal eruptions (such as nonsteroidal anti-inflammatory drugs, viral infections, and food additives) the cornerstone of therapy is antihistamines in up to four times the licensed dose (3). If symptoms are not controlled by antihistamines alone, most patients need immunomodulatory drugs such as systemic glucocorticoids or cyclosporine A. Recent studies show a tremendous effect of omalizumab, a monoclonal antibody against human IgE in antihistamine refractory patients with CU (4, 5). However, due to the lack of pharmacy-supported studies on omalizumab in CU, there is still no agreed-upon dosing schedule for the drug for that indication.

Here we report on the use of omalizumab in four of our patients with CU in 2014, estimate the proportion of CU patients that are candidates for such treatment, and discuss the dosing schedules used in various published studies.

Methods

First, we estimated the number of patients with antihistamine-resistant CU that were referred to a tertiary allergy center. We reviewed the medical files of patients referred for the first time in 2013 and discharged with a diagnosis of L50.0 to L50.9 according to ICD-10.

Second, we report on four patients that are currently (August 2014) being treated at our clinic with omalizumab for CU. Third, we reviewed clinical articles on the use of omalizumab in patients with CU. We identified articles by a PubMED search on July 2014.

Results

In 2013, 323 patients with urticaria were referred, among them 158 (49%) with CU (65% female, median age 37 years, range 18-82). The majority of patients were controlled completely with antihistamines (41% as needed, 25% with a regularly licensed dose, 17% with four times the licensed dose). Fourteen percent of patients were not controlled despite four times the licensed dose of antihistamine (6%) or even the addition of systemic steroids or cyclosporine (8%).

[1]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia. ✉Corresponding author: mitja.kosnik@klinika-golnik.si

Case reports

Case 1: KM, a female currently 31 years old, developed CU with angioedema in 2002. CU was aggravated by physical stimuli. She has allergic rhinitis, sensitized with house dust mite and grass pollen. Thyroid function was normal, thyroid and antinuclear antibodies were absent, there were no signs of chronic infection, and skin biopsy was without signs of vasculitis. The concentration of C3 and C4 components of the complement system were normal. Treatment with a high dose of antihistamines was not successful. She received multiple short courses of systemic steroids. In 2007, cyclosporin was started and continued until 2010, when it was replaced by methotrexate for 6 months. The clinical course of CU improved, but without complete remission. In August 2011 she started with omalizumab (300 mg every 4 weeks). After the first application of omalizumab, almost complete remission of CU was achieved. The interval between applications of omalizumab was gradually increased. At present she is receiving 300 mg of omalizumab every 8 to 9 weeks. She is still almost symptom-free, without antihistamine, with only a few hives only 8 weeks after the application.

Case 2: SM, a female currently 51 years old, was diagnosed with CSU in 2009 after several months of repeated treatment at the local emergency department and primary care physician for episodes of anaphylaxis caused by an unknown allergen. At diagnosis she was already on regular treatment with a systemic steroid. Her symptoms were controlled with a regular daily regimen, but tapering resulted in reappearance of the symptoms. H1 antihistamines at four times the licensed daily dose were prescribed. The addition of H2 antihistamine and montelukast was not effective. She received a trial of methotrexate and cyclosporine therapy, none of which were effective. She developed drug-induced arterial hypertension, osteoporosis, and adrenal insufficiency. After the first dose of 150 mg of omalizumab in October 2013, she was symptom-free for the next 2 weeks, when she received 75 mg. During a 6-month follow-up we concluded that she needs 150 mg of omalizumab every 4 to 6 weeks with concomitant antihistamines in a double licensed dose.

Case 3: KŠV, a 65-year-old female, with ischemic heart disease, Hashimoto thyroiditis, and Raynaud disease, was admitted with a 2-month history of chronic urticaria and angioedema with a UAS of 6/6 in spite of four tablets of desloratadine and montelukast daily. She is regularly on 100 mg of aspirin daily because of vascular stents. She noticed that aspirin aggravates her urticaria. Histology of the hives showed no signs of vasculitis. In July 2014 she received the first dose of 150 mg of omalizumab. After 3 days, the intensity of the urticaria had already decreased, and after 7 days she was able to reduce antihistamines to two tablets daily. Symptoms reappeared after 4 weeks and she needed a new dose of omalizumab.

Case 4: BJ is a 35-year-old female with urticaria and angioedema that started a year and a half ago. The disease was exacerbated during pregnancy. Despite three tablets of loratadine daily, she also needed 8 mg of methylprednisolone daily. After consultation with gynecologists, we offered the patient treatment with 150 mg of omalizumab. Episodes of angioedema ceased after 2 days. Over the following 6 weeks she needed four to five tablets of loratadine weekly because of mild pruritus. Thereafter symptoms returned and she was given a further dose of 150 mg of omalizumab.
We did not notice any side effects of omalizumab in our CU patients.

Literature review and discussion

We presented four patients with severe antihistamine-resistant CSU. All patients responded with nearly complete disappearance of symptoms after omalizumab treatment in a dose of no more than 150 mg/month. We also showed that omalizumab should be considered in up to 14% of CU patients referred to a tertiary clinic.

In allergic diseases, omalizumab is thought to interfere with allergen-induced mast cells and basophil activation. Because CU is not an allergic disease, the mechanisms of actions of omalizumab in CU are not entirely clear (6). There are some actions of omalizumab that are not dependent on the presence of allergen. Monomeric IgE potentiates the activities of mast cells in the absence of allergen cross-linking. Monomeric IgE bind on high-affinity receptors on mast cells and basophils (FcεRI) and influence their differentiation, proliferation, survival, and mediator and cytokine generation. Sensitization of human mast cells with monoclonal IgE alone, without FcεRI cross-linking, was found to upregulate 58 genes including those for cytokines, colony-stimulating factors, chemokines, and cytokine and chemokine receptors (7). Highly cytokinergic (HC) IgE enhance survival, degranulation, adhesion, migration, and expression of cytokines. Poorly cytokinergic IgEs mediate these effector functions inefficiently (8).

There is a strong correlation between CSU and autoimmune diseases (9). Many patients produce IgG autoantibodies against FcεRI, IgE, or both, which can cross-link FcεRI and activate mast cells and basophils (10). Many patients also produce HC IgE antibodies against autoantigens (double- and single-stranded DNA, b-galactosidase, histamine-releasing factor, and thyroglobulin) (11). These findings suggest that autoantibodies such as IgE anti-dsDNA and IgE autoantibodies against thyroid peroxidase (TPO) can also activate basophils to degranulate and play substantial roles in the pathogenesis of CSU.

By binding serum IgE molecules, omalizumab indirectly decreases the number of FcεRI molecules on mast cells / basophils.

Omalizumab can therefore control CU:

- By sequestering monomeric IgE, omalizumab reduces their priming effect on mast cells;
- In patients with IgG autoantibodies against IgE or FcεRI, the depletion of mast cell–bound IgE by omalizumab and consequent downregulation of FcεRI on mast cells and basophils, the concentration of complexes of FcεRI-IgE on mast cells/basophils decreases (12);
- In patients with IgE against autoallergens, the inhibition of IgE binding to FcεRI by omalizumab and the downregulation of FcεRI would represent a central mechanism of omalizumab.

The first report on the use of omalizumab in CU was published in 2006 by Boyce, who successfully treated a patient with cold-induced urticaria (13). In 2007, Spector and Tan published a case series of omalizumab treatment of three patients with CSU (14). Asero published a case report on successful treatment of a child (15).

In early studies, the doses of omalizumab for CU were calculated according to schedules used for treating allergic asthma. Later it was shown in a prospective double-blind study randomizing 323 patients with an average UAS7 of 31 that omalizumab effectiveness in CU is not dependent on concentration of total IgE (4). Patients received three injections of omalizumab or placebo 4 weeks apart. Doses of 150 and 300 mg per month were significantly more effective than placebo with no further improvement when using 600 mg/month. Short-term treatment with omalizumab did not influence the long-term course of the disease. Another 6-month study with 336 patients with similar severity of CIU compared a 300 mg dose with placebo and showed similar results (5). The most recent double-blind study with 318 patients of similar sever-

ity showed that even a 75 mg monthly dose is superior to placebo and of similar efficacy as 150 mg, with a 300 mg dose being more efficient (16). All studies showed a good safety profile of the drug.

Further data on efficacy and dosing schedules were drawn from case series of patients treated in real-life settings. We referred to the article by Ivyansky et al., who reviewed studies published until 2011 (17). We overviewed studies published after that period (Table 1) (17-30). Due to the high price of the drug, the majority of researchers were looking for the lowest dose and longest dosing interval of omalizumab that were effective in inducing symptom control in the majority of patients. Those studies included 470 patients. The results of case report series are rather difficult to compare. There were differences in severity of disease at inclusion. Studies used different definitions of response to therapy, different scoring systems for assessing urticaria activity, and different dosing schedules. Early studies used dosing schedules as proposed for treatment of asthma; however, after dose-response studies that showed that the response to omalizumab is not dependent

Table 1 | **Overview of case series using omalizumab in chronic urticaria.**

Study	Number of patients	Severity of CU at inclusion	Dosing schedule according to tIgE	Omalizumab dose (mg)	Severity of CU during omalizumab treatment	Patients with significant response	Patients with no response	Antihistamine treatment during omalizumab treatment (no. of patients)	Side effects
Ivyansky (17)	19 (1 with delayed pressure urticaria)	NS 14 pts needed prednisolone, 7 azathioprine, cyclosporine A and/or mycophenolate, 6 anti-TNF-α	No	150 mg / 2 w	NS	16	3	NS	3 (headache, nausea); 1 discontinuation of treatment
Godse (18)	5	UAS 4.9–5.5	Yes	300 mg / 2–4 w	UAS 0–1.1	5	0	3	2 headache
Groffik (19)	9	UAS7 35–42 TS 4–5	Yes	5 pts 150 mg / 4 w 4 pts 300 mg / 2–4 w	Mean UAS7 not reported TS 0 (3 pts)–2 (4 pts)	9 (5 with UAS 0 after 4 injections)	0	6	No
Nam (20)	26 (13 with CIndU or angioedema)	UAS-Nam 12.1 ± 2.0 CU-QOL 34.6 ± 13.6	Yes	NS	UAS-Nam 2.7 ± 4.2 CU-QOL 62.6 ± 8.7	22 (10 pts in 4 w)	2	7	4 (mild: facial rash, dyspepsia, weight loss, generalized edema
Viswanathan (21)	19	NS	No	300 mg / 4 w	NS	17 (9 CR)	2	NS	NS
Silva (22)	5	UAS 4–6	Yes	300 mg / 4–6 w	UAS 0	5 (4 after first dose)	0	2	No
Armengot-Carbo (23)	15	NS	No	8 pts: 150 mg / 4 w 7 pts: 300 mg / 4 w	NS	12	3	12	2 (nausea)
Song (24)	16	UAS7 › 35	No	150 mg / 4 w	10 pts UAS7 0 (after first dose)	11 (4 pts were able to discontinue omalizumab)	5	NS	1 (urticaria)
Labrador-Horrillo (25)	110 (including CIndU)	UAS 5.34 ± 0.88	No	54 pts 150 mg / 4 w; 56 ≥ 300 mg / 4 w	UAS 0.66 ± 1.3	90 CR (22 were able to discontinue omalizumab);12 partial response	8	66 pts discontinued antihistamines	No
Kai (26)	15 (6 with cholinergic urticaria and 1 with UV)	UAS7 ≥ 28/42 DQLI ≥ 20/30	Yes	NS	Marked improvement	5 CSU, 6 CIndU 1 UV	3	NS	1 (urticaria)
Lefévre (27)	15	UAS7 31.1 DQLI 13.4	Yes	8 pts 150 mg / 4 w; 7 pts 300 mg / 4 w	UAS7 8.0 DQLI 3.8 after 4 w	14	1	12	2 (headache, nausea)
Uysal (28)	27	UAS 6	No	15 pts 150 mg / 5–8 w; 12 pts 300 mg / 4–8 w	UAS ‹ 2	23	4	All	NS
Sussman (29): Toronto group	34	UAS7 28.1 MS 12.8	No	150 mg / 2–28 w	UAS7 5.7; (in 27 pts UAS7 = 0, 15 pts after first injection) medication score 2.5	30	4	NS	No
Sussman (29): Quebec group	28 CSU; 6 cold urticaria	UAS7 24.4 MS 13.3	No	26 pts 150 mg / 4 w; 10 pts 300 mg / 4 w (7 because of concomitant atopic disease)	UAS7 2.2; (in 16 pts UAS7 = 0, 5 pts after first injection) medication score 3.0	27 CSU; 6 cold urticaria	1	NS	No

Table 1 | **Continued.**

Study	Number of patients	Severity of CU at inclusion	Dosing schedule according to tIgE	Omalizumab dose (mg)	Severity of CU during omalizumab treatment	Patients with significant response	Patients with no response	Antihistamine treatment during omalizumab treatment (no. of patients)	Side effects
Metz (30)	30 CSU	UAS7 25.3	No	19 pts 150 mg / 4–8 w; 11 pts 300 mg / 4 w	NS	25 complete (12 in 1st w), 3 significant	2	5	1 (angioedema)
Metz (30)	34 CIndU	NA	No	13 pts 150 mg / 4–8 w; 8 pts 300 mg / 4 w; 2 pts 450 mg / 4 w	NA	24 complete (12 in 1st w), 4 significant	6	NS	No

CSU = chronic spontaneous urticaria
CindU = chronic inducible urticaria
UV = urticarial vasculitis
tIgE = total IgE
NS = data not stated in the source article
NA = not applicable
UAS = daily urticaria activity score (2); maximum result is 6
UAS7 = Weekly urticaria activity score (2); maximum result is 42
UAS-Nam = daily urticaria activity score measuring pruritus and four characteristics of wheals (number, distribution, mean diameter, duration); maximum result is 15 (31)
CU-QOL = validated 17 items scoring system for measuring quality of life (32); maximum result is 68, higher score indicates higher QOL
DQLI = Dermatology Life Quality Index (33); maximum result is 30, higher score indicates lower QOL
TS = Treatment score (19): a need for concomitant therapy (0 = no symptoms / no therapy, 1 = no symptoms with antihistamines on demand, 2 = no symptoms with daily use of antihistamines in up to fourfold licensed dose, 3 = recurrent symptoms under antihistamines in combination with leukotriene antagonists and/or H2-antihistamines, 4 = no symptoms under immunosuppressive treatment (e.g., corticoid, dapsone), 5 = recurrent symptoms under immunosuppressive treatment)
MS = medication score (29): the sum of weighted scores for the use of antihistamines (regular dose, 2 points; four times the regular dose, 8 points), oral glucocorticoids (‹ 11 mg, 5 points; 11–25 mg, 10 points; › 25 mg, 15 points), cyclosporine 3.0 mg/kg (8 points), hydroxychloroquine (6 points), montelukast (2 points)

on total IgE, researchers tended to use lower doses.

Viswanathan et al. showed that omalizumab was effective regardless of autoimmune status, age, gender, IgE levels of patients with refractory CU, or dosing protocol (21).

Kai et al. studied the effect of omalizumab treatment interruptions on quality of life (26). At inclusion, all patients had UAS7 ≥ 28/42 and Dermatology Life Quality Index (DLQI) ≥ 20/30. Patients were treated with omalizumab in 6-month periods to assess whether their urticaria had gone into natural remission or required further treatment. The breaks between cycles lasted between 1 and 8 months. Symptom control with omalizumab markedly improved quality of life. Some patients were able to return to work. Urticaria relapsed with a median time of 5 weeks in all but one patient after treatment cessation. The DLQI increased in two patients with subsequent treatment cycles, reflecting a tendency for patients to feel more compromised by their illness after experiencing almost complete remission of symptoms during treatment. The authors support the use of continuous rather than periodic omalizumab in patients with severe treatment-refractory CU.

Uysal et al. tried to optimize the dosing protocol to decrease the frequency of hospital visits, making treatment more cost-effective (28). They began treatment with 150 mg of omalizumab every 2nd week. When the average daily UAS score was less than 2, the following dose interval was prolonged. If the patient had a UAS score of 2 or more after two or three injections of the same dose, the time interval to the next injection was reduced and continued at the longest effective ''maintenance'' interval. In patients with UAS > 3 after two to three doses, the dose was increased to 300 mg. Patients that had full remission of symptoms after three doses of omalizumab injections with 8-week intervals had their treatment paused but were monitored closely for any recurrence of symptoms. In the case of recurrence, treatment was restarted and continued with an interval of 8 weeks.

Sussman et al. (29) included patients fulfilling any of the following criteria: UAS7 higher than 30 or a history of repeated administration of oral corticosteroid use or lack of adequate response to recommended treatments. The initial dose was 150 mg subcutaneously every 4 weeks for three to five treatments. If patients responded to treatment, the dosing interval was individualized as required. Patients that achieved complete remission had their treatment discontinued until they had symptoms. Remission was defined as a complete absence of urticarial lesions and pruritus (UAS7 = 0). Use of concomitant medications was documented using quantitative medication score assessments (Table 1).

In a recent retrospective analysis, Metz et al. defined a complete response to omalizumab as a reduction of 90% or more in the UAS7 with no need for antihistamines (30). A reduction in the UAS7 of 90% to 30% was regarded as a significant improvement. An initial dose of 150 mg was used. The dose was adapted according to response to therapy. The study confirmed the rapid onset of action of omalizumab: in 12 out of the 21 CSU patients, complete control of symptoms was reached within the first 24 h.

Similar responsiveness to omalizumab was also shown in patients with CIndU. Patients with dermographism and delayed pressure urticaria were more sensitive to omalizumab (13 out of 15 patients showed a complete response) than patients with cold and cholinergic urticaria (3/6 and 6/8 respectively showed a complete response). Patients with cholinergic urticaria needed a higher dose of omalizumab (the mean dose was 360 mg every 4 weeks).

Twenty-five patients had concomitant angioedema. Angioedema was controlled during omalizumab treatment in parallel with urticaria. The outcome of the treatment was independent of serum IgE levels. Based on their experience, Metz et al. proposed starting treatment with 150 mg of omalizumab. The response is assessed after 4 weeks. In complete responders, 150 mg of omalizumab should be repeated. Then the patients are down-dosed. By reducing the dose and increasing the interval between doses, the optimal and lowest possible individual dose should be determined. In poor responders, the dose should be increased to 300 mg and the response assessed 2 weeks later, when a further 300 mg is given if necessary. If there is a no significant response after a further

2 weeks, treatment with omalizumab should be discontinued.

To conclude, omalizumab should be offered to patients with disturbing itch (itch component of UAS7 of 8 or more) while on a maximum antihistamine dose and patients with a need for immunomodulatory drugs (16). The results of studies indicate that the majority of patients with refractory CU, whether spontaneous or induced, as well as angioedema, respond to a dose of 150 mg of omalizumab once monthly. The response is rapid, being obvious in days, with half of patients being able to stop all other medications, including antihistamines. About 10% of patients do not respond to treatment. The duration of treatment is not known. Ten to 20% of patients are able to discontinue omalizumab treatment; however, in the majority of patients, disease relapses after discontinuation of omalizumab. According to those data and our own experience, it seems prudent to start the treatment with a low dose of omalizumab (150 mg once every 4 weeks), extend the dosing interval in patients with no or minimal symptoms or step up in patients whose urticaria is not sufficiently controlled. Extending the dosing interval to the point of symptom reappearance is important for detecting the 20 to 25% of patients that attain remission of CU and are able to stop treatment with omalizumab.

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