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Use of omalizumab in the treatment of chronic urticaria

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Key words

chronic spontaneous urticaria; omalizumab; treatment; anti-immunoglobulin E; wheal

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Summary

Background. *Omalizumab is indicated to treat chronic spontaneous urticaria (CSU) refractory to antihistamines. We aim to describe the experience of our department in the treatment of CSU with omalizumab.* ***Materials and Methods.*** *Retrospective review of the clinical records of patients.* ***Results.*** *Six patients (5 females, median age 33 years) treated with omalizumab for a median of 17.5 months were evaluated. All patients had improvement of symptoms after the first dose. In one case, the treatment was suspended after 7 months, but in 9 weeks there was recurrence of symptoms. The main side effect was headache in the drug administration's day. Currently, all patients maintain therapy with omalizumab and are clinically stable.* ***Conclusion.*** *Omalizumab proved to be an effective and safe drug for the treatment of patients with refractory CSU.*

Background

Urticaria is a disease characterized by the development of wheals (hives), angioedema or both, and is divided into acute and chronic forms (≥ 6 weeks), with chronic urticaria being further classified into chronic spontaneous urticaria (CSU) and inducible urticaria (1). CSU is the spontaneous development of symptoms with no external specific trigger (2), and inducible urticaria may coexist with CSU (3).

The exact prevalence of chronic urticaria depends on the population studied, but reports suggest that globally it can affect up to 1% of the population at any given time (2). CSU accounts for approximately two-thirds of the cases of chronic urticaria (4), with the peak incidence in working age (20-40 years-old) (5), and the duration of chronic urticaria in adults has been reported to be as follows: 6-12 weeks in 52.8%, 3-6 months in 18.5%, 7-12 months in 9.4%, 1-5 years in 8.7% and over 5 years in 11.3% (6).

CSU has a high overall impact on quality of life (2). Patients who suffer from this disease have a high disease burden, because of the associated impact on physical, emotional and social aspects of their life (2). Further, there is a high socioeconomic impact arising from both the direct costs (such as medication or healthcare visits) and indirect costs (such as absence or reduced efficiency at work) (2).

With respect to the treatment of urticaria, the international EAACI / GA2LEN / EDF / WAO guidelines state that the aim of therapy should be complete symptom control (1). In CSU, the recommended first-line treatment option is non-sedating H1-antihistamines, which are only effective in around half of the patients (3). The second-line treatment recommended is a trial of up to fourfold dose of second generation H1-antihistamines (1), which reduce symptoms in about 75% of patients with chronic urticaria (including patients with concomitant inducible urticaria) (7). In the remaining cases, third-line treat-

ments must be considered, namely the use of monoclonal antibodies, as omalizumab (1).
Based on Phase III clinical data in patients with CSU, omalizumab was approved in Europe in February 2014 as a third-line therapy for the treatment of CSU in adult and adolescent patients showing an inadequate response to H1-antihistamine treatment (2), being the dosage either 150 or 300 mg subcutaneously every 4 week.
Omalizumab is a recombinant, humanized, monoclonal, anti-IgE murine antibody that targets the C3 domain of the Fc region of IgE, reducing the levels of free IgE by sequestration what can also, indirectly, cause the downregulation of the cell-surface FcεRI receptors, which may reduce the potential for histamine release and the subsequent symptoms of CSU (2,8,9).
The aim of this study is to describe the experience of our department in the treatment of refractory chronic urticaria with omalizumab and to assess its efficacy and safety.

Materials and methods

We performed a retrospective review of the clinical records of patients treated with omalizumab in our department, from November 2012 to June 2015, in the context of severe chronic urticaria. The baseline characteristics of patients before starting the treatment and their clinical evolution were evaluated.
Prior to initiation of anti-IgE treatment all patients signed an informed written consent, and the administrations of omalizumab were performed under medical supervision, with a time of surveillance of 2 h after the first three administrations and 30 minutes thereafter.
After starting anti-IgE antibody, corticosteroids were weaned as tolerated. Response to the therapy was assessed based on the time until improvement of symptoms and the weaning of corticosteroids. The number of exacerbations after starting omalizumab that required treatment with corticosteroids was assessed as well as the side effects of anti-IgE therapy.

Results

We studied 6 patients (5 females and 1 male) with a median age of 32 years-old (range 22-61). The baseline characteristics of the patients and their clinical evolution are presented in **table 1**. They all had chronic spontaneous urticaria, that in one case was associated to inducible urticaria (dermographic, cholinergic and delayed pressure urticaria) and the median duration of symptoms was 8 years (range 2-20). All patients had recurrent attacks of generalized urticaria, with almost daily moderate to severe symptoms before starting omalizumab.
Patient 2 had a confirmed hypersensitivity to anti-histamines and corticosteroids. She referred development of urticaria lesions and angioedema when taking multiple antihistamines (loratadine, desloratadine, cetirizine and promethazine) and corticosteroids (hydrocortisone, methylprednisolone and deflazacort). We performed a single-blind drug challenge with placebo which was negative. and single-blind drug challenges with suspected and alternative antihistamines (desloratadine and dimethindene) that were both positive. It was also conducted a single-blind drug challenge with an alternative corticosteroid (dexamethasone) which was negative, but latter the patient was treated with dexamethasone and developed urticaria with angioedema. Therefore, patient 2 had no alternative medication to treat CSU and thus started treatment with omalizumab.
The other cases showed poor response to treatment with maximal doses of anti-histamines (four-time updosing) and required frequent cycles of daily oral corticosteroid to achieve symptomatic control. Additionally, patient 5 had previously been treated with cyclosporine (2 months, 0.6 mg/kg), and sulfasalazine (2 months, 1500 mg/daily) which were not effective.
Four patients were atopic and 3 had allergic asthma and rhinitis. The anti-thyroid antibodies were positive in 1 case (anti-thyroid peroxidase antibodies - 46 UI/mL) and the thyroid function test was compatible with hypothyroidism in another one. Total serum IgE was elevated in 5 patients (median value 316 IKU/L, range 28-1055). The autologous serum skin test was performed in 2 cases and it was positive in one.
In patient 6, who initiated anti-IgE antibody in the year of 2012, the initial dose of medication used was calculated according to the patient's bodyweight and total serum IgE (300 mg bimonthly), as performed in the cases of severe asthma. In the other patients, who started treatment between November 2013 and February 2014, after the publication of the likely optimal doses of omalizumab for treatment of chronic urticaria (10), the initial dose used was 300 mg monthly.
The median duration of treatment was 17.5 months (16-31) and there were no dropouts. All patients showed improvement of symptoms after the first administration of omalizumab and it was possible to discontinue corticosteroids before the second administration in 4 cases.
Two weeks after the first dose, patient 3 presented an exacerbation of urticaria lesions that required a cycle of corticosteroids for resolution. In the fourth, fifth and eleventh months of treatment, she presented other four symptomatic exacerbations, two of them in the context of antibiotic therapy used in the treatment of skin and urinary tract infections.
In patient 6, four months after adequate control of urticaria with administration of omalizumab 300 mg bimonthly, a decrease in the dose was held to 150 mg monthly, without symptoms recurrence. Three months later, the period between administrations was increased to 5 weeks, but in approximately 4 weeks the patient began experiencing lesions of urticaria. For this reason, administrations at 4 week intervals were resumed.

After 7 months of treatment without recurrence of symptoms, omalizumab was suspended in patient 1. Nine weeks later, she began experiencing lesions of urticaria with incomplete control, so the anti-IgE antibody was restarted with resolution of symptoms after the first administration.
The main side effect observed was headache in the drug administration's day that was found in 2 patients, who improved clinically with analgesics.
Currently, all patients maintain therapy with omalizumab and are clinically stable.

Discussion

In our study we report six patients with severe chronic urticaria who showed a good long-term response to treatment with omalizumab, being possible to discontinue the corticosteroid treatment in all patients.
As observed in other studies (11), the anti-IgE treatment had a rapid onset of action, with relief of urticaria lesions within days to few weeks after first administration. This rapid response may be a reflection of the binding of the omalizumab to free IgE antibodies, which occurs within a few hours of administration that reduces the binding of IgE to the high affinity receptor FcεRI on basophils and mast cells. It may also be related to the downregulation of the expression of FcεRI on blood basophils (within 2 weeks) and mast cells (within 8 weeks) (3,10).
Chronic urticaria patients frequently exhibit increased total IgE levels (12) and have autoimmune conditions, especially thyroid autoimmune disorders, such as Hashimoto thyroiditis (13). Several independent studies have reported that a significant number of patients with chronic urticaria (up to 33% in some studies) exhibit high level of autoantibodies to thyroid antigens (14). In fact, almost all of our patients (5 in 6) showed increased levels of total serum IgE and one also presented Hashimoto thyroiditis, but their response to anti-IgE treatment showed no differences from the other patients.
According to other published case reports and real-life retrospective observational studies, omalizumb has also been reported to be effective in cases of chronic inducible urticaria (1,2,11) such as cholinergic urticaria (15), cold urticaria (16,17), solar urticaria (17), heat urticaria (18), dermographic urticaria (17,19), and delayed pressure urticaria (20). Some of this indications are currently being evaluated in randomized clinical trials (21,22,23).
In our study, the anti-IgE treatment also showed effectiveness in one patient with severe chronic spontaneous urticaria associated to various subtypes of inducible urticaria (dermographic, cholinergic and delayed pressure urticaria). Thus, omalizumab may be a therapeutic alternative in some cases of refractory inducible urticaria.
Currently, the recommendations to guide the use of omalizumab in the treatment of chronic urticaria are a subject of controversy, so the authors' criteria to interrupt treatment, change the dose or increase the duration between doses were based on the clinical course of patients. When disease control was reached and patients were clinically stable, changes in the doses or suspension of the treatment were attempted in order to achieve the lowest effective dose.
In one patient, omalizumab was suspended after 7 months of successful treatment, but in nine weeks we verified recurrence of the urticaria lesions. These results are similar to those found in other studies. Silva PM, et al (24) suspended omalizumab in 3 patients, respectively after 12, 18 and 24 months of successful treatment and all of them, approximately six weeks later, had urticaria recurrence. Two phase III multicenter trials, with follow-up periods of 16 weeks, have also reported the reappearance of urticaria in an average of 10 weeks after discontinuation of omalizumab (10,25). In another study (7), with patients observed for additional 20 weeks after 3 administrations of anti-IgE antibody, at 8 weeks, there was a gradual return of pruritus and urticaria by week 20. This data suggests the need for long term treatment at least for some patients (3).
Since 2006, there have been a number of case reports with scarce number of patients on the use of omalizumab in chronic urticaria and also broader real-life studies (both retrospective and prospective) and some phase III studies (2). In all of them, the treatment was well tolerated and no safety issues or concerns were reported when they were compared with the well-established profile of the anti-IgE treatment use in allergic asthma (10,25,26).
In the six cases here described, only mild side effects were reported in 2 cases (headaches), none of them leading to treatment withdrawal.
The main limitation of this study is related to the limited dimension of our case series which makes it difficult to characterize patients' features that can provide different responses to anti-IgE treatment. However, the clinical improvement seemed to be independent of gender and age, duration of the disease, total serum IgE levels and presence of atopy.
Patient 3 had a less effective response to omalizumab, as she presented 5 exacerbations requiring corticosteroids during omalizumab treatment. The only feature that distinguishes her from the other patients is the presence of positive anti-thyroid antibodies, but other studies have shown efficacy of omalizumab also in cases with positivity to these antibodies (24,27).

Conclusions

Omalizumab seems to be a new effective and safe treatment for patients with chronic urticaria refractory to other treatments. However, some issues regarding its use needs to be addressed in the future and further studies will be necessary. The mechanisms of action of omalizumab have not been fully clarified

Table 1 *- Baseline characteristics of the studied patients and their clinical evolution.*

Patient	**1**	**2**	**3**	**4**	**5**	**6**
Gender	M	F	F	F	F	F
Age (at start of omalizumab treatment)	61	22	25	33	31	39
Duration of symptoms (years)	2	10	5	20	9	7
Angioedema	Yes	Yes	Yes	No	Yes	Yes
Association with inducible urticaria	No	No	No	No	No	Yes[1]
Previous treatments	AH, SC, LTRA	No	AH, SC	AH, SC	AH, SC	AH, SC, LTRA, Cy, Doxepin, Su
Total Serum IgE (IKU/L)	239	320	28	313	1055	548
ASST	NP	–	NP	NP	NP	+
Anti-thyroid antibodies	–	–	+	–	–	–
Atopy	Yes	Yes	No	Yes	No	Yes
Other diseases	Dyslipidemia, Diabetes and hypothyroidism	A+R, DH[2]	DH, Hashimoto thyroiditis	A+R	Adrenal adenoma	A+R, Hypertension
Start of treatment	Nov 2013	Feb 2014	Feb 2014	Dec 2013	Nov 2013	Nov 2012
Inicial omalizumab dose	300 mg 4/4 week	300 mg 4/4 week	300 mg 4/4 week	300 mg 4/4 week	300 mg 4/4 week	300 mg 2/2 week
Duration of treatment (months)	16	17	17	18	19	31
Administrations required to clinical improvement	1	1	1	1	1	1
Administrations required to corticosteroid discontinuation	1	NA	1	1	3	1
Exacerbations requiring corticosteroid treatment	0	0	5	0	1	1
Current omalizumab dose	300 mg 4/4 w	300 mg 4/4 w	300 mg 4/4 w	300 mg 4/4 w	300 mg 4/4 w	150 mg 4/4 w
Current additional medication	AH on demand	AH on demand	AH 3xday	AH on demand	AH on demand	AH 4xday
Side effects	None	None	None	None	Headache	Headache

F - Female; M - Male; AH - anti-histamine, SC - systemic corticosteroid; LTRA - Leukotriene receptor antagonist; Cy - Cyclosporine; Su - Sulfasalazine; ASST - Autologous serum skin test; NP - Not performed; A+ R - Asthma and rhinits; DH - Drug hypersensitivity; NA - Not applicable; AH - Anti-histamine; w - Week.

[1]Dermographic, cholinergic and delayed pressure urticaria

[2]Hypersensitivity to anti-histamines and corticosteroids

and also the duration of treatment remains to be established (3). Similar to other medications and interventions, the decision to continue omalizumab for chronic urticaria should include assessing therapeutic benefit and any untoward effects (3).

During the treatment, attempts should be made to achieve the lowest dose that allows the control of symptoms. Instead of reducing the dose given every month, the authors consider a better alternative to increase the interval between the doses, since this approach allows more comfort to patients, reducing the hospital visits. Other reasons that justify trying to achieve the lowest effective dose are the high cost of omalizumab as well as the possible occurrence of long-term side effects not yet known.

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