



Contents lists available at ScienceDirect



Real-life experiences with omalizumab for the treatment of chronic urticaria

Gordon Sussman, MD^{*}; Jacques Hébert, MD[†]; Carly Barron, HBSc^{*}; Jia Bian, HBSc^{*}; Rose-Marie Caron-Guay, RN[†]; Stéphanie Laflamme, RN[†]; and Simon Stern, HBSc^{*}

^{*} Division of Allergy and Clinical Immunology, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

[†] Centre de recherche appliquée en allergie de Québec, Laval University, Quebec City, Quebec, Canada

ARTICLE INFO

Article history:

Received for publication September 12, 2013.

Received in revised form November 28, 2013.

Accepted for publication December 3, 2013.

ABSTRACT

Background: Evidence has shown that omalizumab, a subcutaneous anti-IgE monoclonal antibody, is highly effective for the treatment of chronic urticaria.

Objective: To evaluate omalizumab 150 mg/month in severe, difficult-to-treat, chronic urticaria in a real-life setting.

Methods: This prospective open-label study evaluated of 150 mg of omalizumab in severe urticaria defined by a 7-day urticaria activity score (UAS-7) higher than 30, a history of oral glucocorticoid use, and by suboptimal response to previous treatments. Two subgroups of patients at different centers (Toronto and Quebec City, Canada) were included. The primary efficacy evaluation was a change in UAS-7 from baseline. A quantitative medication score assessed the use of other anti-urticarial medications.

Results: Sixty-eight patients were included: 61 with chronic spontaneous urticaria, 6 with cold urticaria, and 1 with urticarial vasculitis. Patients were followed for up to 25 months. In Toronto, mean UAS-7 decreased from 32.2 at baseline to 5.7 after the last omalizumab treatment. Seventy-nine percent achieved complete remission during omalizumab therapy (UAS-7 0) and 6 (18%) showed improvement but never achieved complete remission. The most common maintenance dosing intervals were 1 to 3 months. In Quebec City, from baseline to 18 months, mean UAS-7 decreased from 24.4 to 2.2 and the quantitative medication score decreased from 13.3 to 3.0. All 6 patients with cold urticaria became symptom free, with a significant decrease of their cold stimulation tolerance test.

Conclusion: Omalizumab 150 mg was effective in difficult to treat patients with severe, chronic urticaria refractory to recommended treatments who usually required prednisone. Omalizumab induced a long-lasting positive response and was well tolerated without side effects.

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Chronic spontaneous urticaria (CSU) is defined as the presence of spontaneously occurring hives and/or angioedema with variable degrees of pruritus for a period longer than 6 weeks.¹ CSU, which was formerly referred to as chronic idiopathic urticaria, is quite common in generalist and specialist practices; the estimated life-time prevalence is 0.5% to 1.0%.² The impact of the condition can be substantial, with patients affected by CSU potentially experiencing substantial disability, decreased quality of life, psychological and emotional distress, and decreased productivity.^{3–5} Although the requirement for chronicity is only 6 weeks' duration, CSU can persist for years; a 2004 study showed that it lasted longer than 1 year in 70% of patients and persisted longer than 5 years in 14%.⁶

Chronic spontaneous urticaria is difficult to treat in many patients. The recommended first-line treatment is a nonsedating

oral H₁-blocking antihistamine, with subsequent dose titration up to 4 times the recommended pharmacologic dose.⁷ However, more than half of patients with CSU do not respond adequately to antihistamines.⁸ Until now, the next-line intervention with quality evidence for efficacy has been cyclosporine A, but its use is limited by the high incidence of adverse events.⁷ Other options with lower-quality evidence include leukotriene antagonists and hydroxychloroquine. According to consensus guidelines, the use of systemic glucocorticoids should be limited to treat exacerbations,⁷ but in real-life clinical practice, the severity and lack of effective treatments have necessitated their long-term use in many patients, which has been associated with many potential toxicities.⁹

There is limited evidence available for effective treatments in patients with cold-induced urticaria who do not respond to antihistamine therapy.⁷

However, evidence emerging during the past several years has supported a role for omalizumab, an anti-IgE monoclonal antibody, in the management of chronic urticaria. These include some observational studies and case reports,^{10–18} a proof-of-concept study,¹⁹ and 4 prospective, randomized clinical trials.^{20–23} A multicenter,

Reprints: Gordon Sussman, MD, 202 St Clair Avenue W, Toronto, ON M4V 1R2, Canada; E-mail: gsussman@rogers.com.

Disclosures: Dr Hébert has been a board member of Merck, Novartis, Pfizer, Sanofi, CSL Behring, and ViroPharma.

Table 1
Patient characteristics

Variable	Total	Toronto	Quebec City
Patients, n	68	34	34
Women/men, n	50/18	23/11	27/7
Age (y), mean (range)	44.7 (7–78)	47.6 (10–68)	42.9 (7–78)
Diagnosis, n/N			
CSU	61/68	34/34	27/34
Cold urticaria	6/68	0	6/34
Urticarial vasculitis	1/68	0	1/34
Duration of urticaria (y), mean (range)	NA	8.2 (0.25–34)	NA
Treatment history, n/N			
Prior use of antihistamines	68/68	34/34	34/34
Prior use of systemic glucocorticoids	66/68	34/34	32/34 ^a
Open prescription for systemic glucocorticoids at omalizumab initiation	31/68	25/34	6/34
Use of other medications at omalizumab initiation, n/N			
Leukotriene antagonists	11/68	0/34	10/34
Cyclosporine	7/68	0/34	7/34
Hydroxychloroquine or methotrexate	14/68	5/34	9/34

Abbreviations: CSU, chronic spontaneous urticaria; NA, data not available.

^aThe 2 patients without a history of systemic glucocorticoid use were those with a diagnosis of cold urticaria.

randomized, double-blinded trial in 323 patients refractory to H₁ antihistamines reported clinically meaningful and statistically significant decreases in itch severity score (primary end point) and improvements in all other studied efficacy end points.²² This study was conducted with patients on only H₁ antihistamine therapy as rescue medication, which suggests a milder form of CSU than those reported herein. In addition, some case reports that have suggested that omalizumab may be useful for the treatment of cold urticaria.^{24–26}

The mechanism of action of omalizumab in chronic urticaria is unknown. Some data have suggested that it exerts its therapeutic effects through downregulation of IgE receptors on mast cells and basophils.²⁷

Methods

Rationale

This is a prospective, real-life study of patients with severe, refractory chronic urticaria treated with omalizumab at 2 Canadian centers (Division of Allergy, Clinical Immunology, St Michael's Hospital, Toronto, Ontario and Clinique d'asthme et d'allergie de Québec, Quebec City, Quebec).

In many of the published omalizumab trials, patients with clinically severe disease have been included, but they were treated only with antihistamines. In real life, many patients who are clinically severe do not respond to first-, second-, or third-line treatments and often require systemic glucocorticoids to achieve comfort. The present study and other recently published work^{18,23} have assessed the effectiveness of omalizumab in this population.

In addition, the present cohort includes a small subset of patients with cold urticaria, a population for which therapeutic options are limited.⁷ As such, the present study adds valuable information to the substantial and growing evidence base for omalizumab for the treatment of urticaria.

Objectives

The objectives of this study were to evaluate omalizumab, at a dose of 150 mg/month, in severe, difficult-to-treat, chronic urticaria, by assessing the impact on clinical severity, time to induce remission, and dose schedule necessary to induce and sustain long-term remission.

Patients

Patients included in this study at the Toronto and Quebec City centers had severe disease as defined by any of the following criteria: 7-day urticaria activity score (UAS-7) higher than 30, a history of repeated administration of oral corticosteroid use, and by the lack of adequate response to recommended treatments. The UAS-7 is a validated tool used to assess urticaria severity.²⁸ Briefly, the symptoms were monitored by numbers of hives (none, 0 point; <10 per day, 1 point; 10–50 per day, 2 points; >50 per day, 3 points) and the intensity of pruritus (none, 0 point; mild, 1 point; moderate, 2 points; severe, 3 points) each day for 7 days, for a maximum total score of 42 points.

Intervention

All patients were treated with subcutaneous omalizumab. The dosing and schedule of the study drug differed at the 2 centers. In Toronto, the dose was 150 mg subcutaneously every 4 weeks for 3 to 5 treatments. Based on the patient's response to these initial doses, alternative dosing frequencies were determined on an on-demand basis. If patients responded to treatment and required maintenance dosing, the dosing interval was individualized as required, often extending to every 6 to 8 weeks. Patients who achieved complete remission had their treatment discontinued until they needed more drug. In the Quebec City cohort, the planned dose was 150 mg of omalizumab per month. Dose adjustments were possible based on clinical response.

The treating physicians made adjustments to concomitant medications according to the clinical response. Patients who were receiving oral glucocorticoids at baseline and who benefited from omalizumab treatment were tapered off oral glucocorticoids as tolerated. The use of non-study medications was documented at baseline and throughout follow-up.

Assessments

The primary efficacy assessment used in each of the 2 centers was the UAS-7, which was collected from patient diaries and compared with baseline. Use of concomitant medications was documented through the review of medical records before baseline and recorded by the treating physicians using quantitative medication score assessments. This represented the sum of weighted scores for the use of antihistamines (regular dose, 2 points; 4 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) and montelukast (2 points).

Time to remission and the dosing interval required to maintain remission were documented. Remission was defined as a complete absence of urticarial lesions and pruritus (UAS-7 0).

Adverse events and serious adverse events were documented by the physicians at each center.

Investigators in the Toronto subgroup obtained approval from the Canadian SHIELD ethics review board. However, for this study, approval from an institutional review board was not necessary, because the analyses were performed on data recorded during the routine treatment of patients. All patients at the 2 centers provided oral informed consent.

Results

Patient Characteristics

Sixty-eight patients with severe chronic urticaria were included in this study: 61 with CSU, 6 with cold urticaria, and 1 with urticarial vasculitis (Table 1). Thirty-four patients (all with CSU) were from the Toronto center and 34 were from Quebec City. All patients were treated with at least 1 dose of subcutaneous omalizumab.

Table 2
Duration of omalizumab treatment

	% (n/N) ^a			
	0–6 mo	6–12 mo	12–24 mo	>24 mo
Overall	53% (36/68)	24% (16/68)	15% (10/68)	7% (5/68)
Toronto subgroup	47% (15/34)	29% (10/34)	9% (3/34)	15% (5/34)
Quebec City subgroup	62% (21/34)	18% (6/34)	21% (7/34)	0

^aDue to rounding, rows may not add up to 100%.

In the Toronto subgroup, mean disease duration was 8.2 years (range 0.25–34 years). Twenty-six of the 34 patients had a documented history of angioedema. Two of the 34 patients had documented concomitant asthma. Approximately two thirds of patients were women (23 of 34) and the mean age was 47.6 years (range 10–68 years).

Of the 34 patients in the Quebec City subgroup, 27 (79.4%) were women and the mean age was 42.9 years (range 7–78 years). Twenty-seven of the 34 patients had a diagnosis of CSU, 6 had cold urticaria (acquired cold urticaria with daily symptoms), and 1 had urticarial vasculitis.

Treatment History

All patients with CSU had been treated previously with H₁-blocking antihistamines and all had a history of treatment with oral glucocorticoids (except patients with cold urticaria; Table 1).

In the Toronto cohort, the most frequently used antihistamine was cetirizine, at doses up to 80 mg/d. Other antihistamines, such as hydroxyzine, doxepin, or desloratadine, were used. Most patients had been on other third-line therapies (eg, hydroxychloroquine, intravenous immunoglobulin, and cyclosporine). At the time of omalizumab initiation, 25 of 34 had an open prescription for prednisone with variable dosages and schedules, including on an as-needed basis.

In the Quebec City cohort, in addition to H₁-blocking antihistamines (agents and doses as those in the Toronto subgroup), patients were being treated with additional therapies at the time of omalizumab initiation, including leukotriene antagonists (10 patients) and cyclosporine (7 patients). The Quebec City patients (except those with cold urticaria or contraindications) who were not on cyclosporine at the time of omalizumab previously had a trial with cyclosporine. Six of the 34 patients had open prescriptions for prednisone at the time of omalizumab initiation.

Omalizumab Treatment

In the Toronto group, 30 of the 34 patients received omalizumab at a dose of 150 mg. Four patients received higher initial doses based on IgE levels. The number of treatments ranged from 2 to 23. The duration of follow-up is presented in Table 2. After a remission was achieved, patients were offered an on-demand schedule, which allowed the capture of treatment intervals. Although some patients received omalizumab at a regular interval once every month (11 of 34 patients, 32%), for the other 23 patients, there was variability in the dosing interval. These patients returned for follow-up omalizumab treatments only if they experienced a flare of their urticaria. The dose interval for the patients who had reached maintenance stage (ie, had received ≥ 5 injections, $n = 14$) was 1 to 3 months for 71% (10 of 14), with an interval range of 2 weeks to 7 months.

In the Quebec City subgroup, 26 of the 34 patients initially received 150 mg/month subcutaneously. Seven patients (including 2 patients with cold urticaria) received 300 mg/month subcutaneously (because of concomitant atopic disease) and the patient with urticarial vasculitis received 150 mg every other week (owing

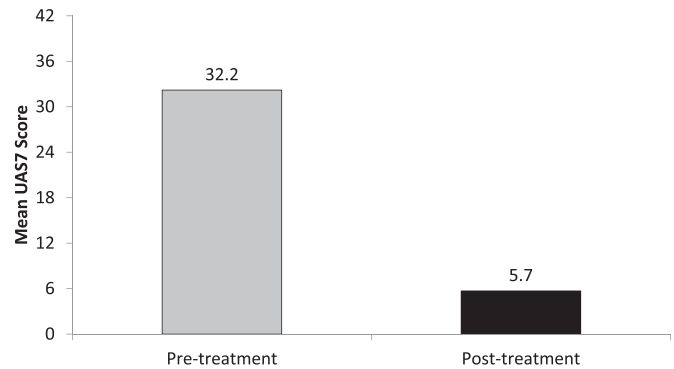


Figure 1. Mean 7-day urticaria activity score (UAS7) before and after omalizumab treatment in the Toronto subgroup.

to a partial response to the first dose). Subsequent dose adjustments were made in 2 patients with CSU: 1 patient's dose was uptitrated to 375 mg every other week at week 10 and the other patient's dose was increased to 300 mg/month after 1 year at the initial dosage. The 2 adjustments were due to an insufficient response to the lower dose. The duration of follow-up was 6 months or shorter for 21 patients (62%), 6 months to 1 year for 6 patients (18%), and 1 to 2 years for 7 patients (21%; Table 2).

Primary Efficacy Variable (UAS-7)

In the patients with CSU or urticarial vasculitis, the mean UAS-7 before omalizumab treatment was 28.1 (32.2 in the Toronto group and 24.4 in the Quebec City group). In the subgroup of patients with cold urticaria, the mean UAS-7 before omalizumab was 16.9, because of cold avoidance strategies.

For the patients in the Toronto subgroup, the mean UAS-7 during the 4 weeks after the last omalizumab treatment was 5.7, an absolute improvement of 26.5 points (Fig 1). Twenty-seven of the 34 patients (79%) achieved complete remission (UAS-7 0) at some point during omalizumab therapy. Fifteen patients achieved remission after the first injection, 6 after the second, 4 after the third, and 2 after the fourth. Six patients (18%) showed improvement but did not achieve complete remission. One patient was completely refractory to omalizumab and 3 additional patients who initially responded (2 with complete remissions and 1 with improvement without remission) became refractory to omalizumab during the period of observation.

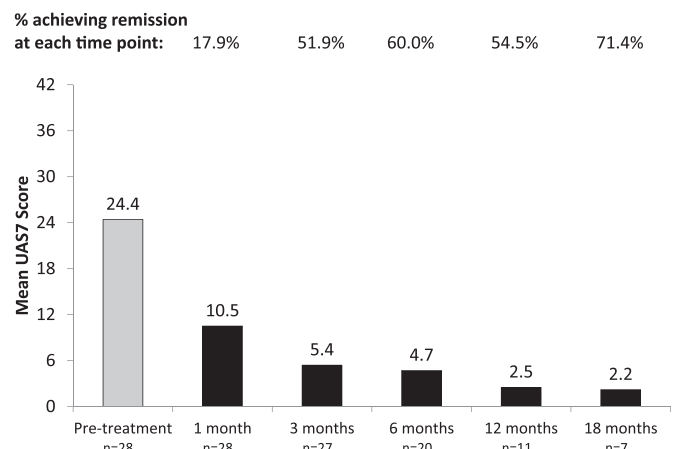


Figure 2. Mean 7-day urticaria activity score (UAS7) and proportion of patients achieving remission over time in the Quebec subgroup.

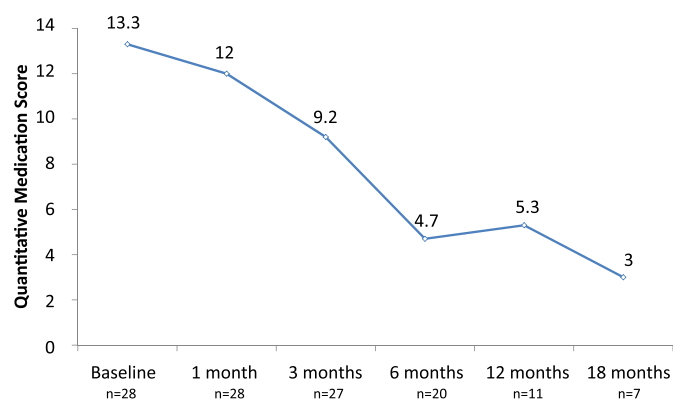


Figure 3. Decrease in quantitative medication by time since omalizumab initiation in the Quebec City subgroup.

In the Quebec City subgroup, overall mean UAS-7 decreased substantially from before treatment through to 18 months. The mean scores during this period were (excluding patients with cold urticaria) 24.4 before treatment, 10.1 at 1 month, 5.4 at 3 months, 4.7 at 6 months, 2.5 at 12 months, and 2.2 at 18 months (Fig 2).

Sixteen of 28 patients in this subgroup (57%) achieved complete remission during follow-up. Eleven more patients showed improvement on omalizumab therapy but did not achieve remission. One patient did not experience any meaningful improvement and discontinued omalizumab therapy after 3 months. The proportions of patients who achieved remission (UAS-7 0) were 17.9% (5 of 28) at 1 month, 51.9% (14 of 27) at 3 months, 60.0% (12 of 20) at 6 months, 54.5% (6 of 11) at 12 months, and 71.4% (5 of 7) at 18 months.

Cold Urticaria: Cold Stimulation Tolerance Test

In the subgroup of 6 patients with cold urticaria, all became symptom free on omalizumab, with a significant decrease of their cold stimulation tolerance test results.

Concomitant Medication Use

In the Toronto cohort, the mean medication score at the time of omalizumab initiation was 12.8. The mean baseline medication score in the 28 Quebec City patients (excluding those with cold urticaria) was 13.3.

Overall and in the 2 subgroups, omalizumab therapy led to a decrease in the use of concomitant medications. In the Toronto subgroup, after omalizumab therapy, the mean medication score was 2.5 (change from baseline –10.3). Of the 25 patients who had a prescription for prednisone at the initiation of omalizumab therapy, 7 patients continued to require prednisone during the omalizumab treatment period. Four of these patients required prednisone only when the effects of omalizumab had worn off and they responded to additional injections. Three other patients, although they initially responded with partial (1 patient) or complete (2 patients) remission, became refractory and maintained their prednisone doses. In the Quebec City group, the quantitative medication score decreased from 13.3 at baseline to 12.0 at 1 month, 9.2 at 3 months, 4.7 at 6 months, 5.3 at 12 months, and 3.0 at 18 months (Figure 3). Of the 6 patients who were on prednisone at baseline, 4 were able to discontinue the oral glucocorticoid completely, 1 was able to lower the dose from 10 to 5 mg, and 1 maintained a 10-mg dose.

Safety Observations

No serious adverse events were reported during the study.

Discussion

This study was carried out to assess the efficacy of omalizumab, at a low dose, in patients with severe chronic urticaria not responding to recommended therapies and often requiring systemic steroids to control exacerbations, as seen in a real-life setting. Two centers were involved, using slightly different approaches: in Toronto, a positive response was induced with monthly treatment and then patients were given the opportunity to continue on an on-demand basis. In Quebec City, patients were treated regularly on a monthly basis. The clinical response was assessed by measuring clinical activity using the UAS-7 system and by monitoring the use of concomitant medication.

Most patients with CSU experienced a remarkable response to omalizumab: 43 of 62 (69%) achieved complete remission. This positive clinical response was accompanied by decreases in other anti-urticarial medications, including glucocorticoids. Indeed, only 8 patients required systemic glucocorticoid therapy, 4 of whom, from the Toronto group, used prednisone only as a bridging intervention until the next omalizumab dose was administered. Significant clinical responses to omalizumab in chronic urticaria have been reported previously, but the present patients had symptoms that were more severe than in most other published studies, in which patients were significantly affected clinically but were not on medication during the observation period. The present group would not have been able to remain free of medication for any period. Most patients had been on glucocorticoids at some point, and many had open prescriptions for systemic glucocorticoids, which they used when needed.

The present results also support the efficacy of the 150-mg dose every 4 weeks for chronic urticaria despite disease severity. Of the 43 patients who achieved remission in the present study, 40 were treated with the 150-mg dose. Although good results were seen in patients who received their injections of omalizumab on a fixed schedule, patients in the on-demand Toronto subgroup whose response disappeared and showed flare-ups at variable times after their last dose of omalizumab could recapture their response with a subsequent injection. These observations suggest that fixed and on-demand dosing strategies are viable alternatives for omalizumab therapy in severe CSU.

In addition, it is important to remember that this study was self-funded and patients in the Toronto subgroup were completely responsible for the costs of therapy (approximately Can \$700 per 150-mg injection in the province of Ontario). For Quebec City patients, drug costs were reimbursed by private or public insurers, each of whom had to be convinced of the therapeutic value of omalizumab before the drug could be approved for this use. Despite these limitations, 68 patients were enrolled. The fact that almost all patients stayed on omalizumab reflects the effectiveness of this intervention compared with the options they had tried previously.

Moreover, in the present cohort, patients were observed for a longer period than in most other reported studies (up to 25 months). The sustained efficacy and lack of serious adverse events during this period are encouraging observations for this intervention and provide further support for long-term use of this intervention. However, it should be noted that few patients (5 of 62, 8%) became refractory to treatment.

Further, the response to omalizumab in the small group of patients with cold urticaria was noteworthy. All 6 of these patients became asymptomatic and showed a significantly improved skin reaction to the cold stimulation tolerance test. Although the number of patients was small, this remains an encouraging development in this subset of patients with urticaria for whom treatment options are limited.

In conclusion, the present real-life study adds to the growing evidence base in support of the use of omalizumab for chronic urticaria. This evolving evidence base heralds a paradigm shift in

the treatment of these patients. The compelling data from research with omalizumab, including the data for patients with the severe form in the present study, show that many of these previously difficult-to-treat patients can achieve complete, sustained responses while being spared from the toxicity associated with oral glucocorticoids. Future updates of clinical practice recommendations should consider the key results of this study: despite severe disease, a 150-mg dose of omalizumab was sufficient to induce complete remission in most patients, and maintenance doses could be given every 6 to 12 weeks.

Acknowledgment

Assistance with the writing and editing of the report was provided by medical writer Scott Moffatt on behalf of Agence liV, Montreal, Quebec. The fees for this service were paid by the authors.

References

- [1] Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*. 2009;64:1417–1426.
- [2] Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy*. 2007;37:631–650.
- [3] Barbosa F, Freitas J, Barbosa A. Chronic idiopathic urticaria and anxiety symptoms. *J Health Psychol*. 2011;16:1038–1047.
- [4] Engin B, Uguz F, Yilmaz E, Ozdemir M, Mevlitoglu I. The levels of depression, anxiety and quality of life in patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol*. 2008;22:36–40.
- [5] Thompson AK, Finn AF, Schoenwetter WF. Effect of 60 mg twice-daily fexofenadine HCl on quality of life, work and classroom productivity, and regular activity in patients with chronic idiopathic urticaria. *J Am Acad Dermatol*. 2000;43:24–30.
- [6] Toubi E, Kessel A, Avshovich N, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy*. 2004;59:869–873.
- [7] Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009;64:1427–1443.
- [8] Kaplan AP. Treatment of chronic spontaneous urticaria. *Allergy Asthma Immunol Res*. 2012;4:326–331.
- [9] Schellenberg R, Adachi JD, Bowie D, et al. Oral corticosteroids in asthma: a review of benefits and risks. *Can Respir J*. 2007;14(suppl C):1C–7C.
- [10] Groffik A, Mitzel-Kaoukhov H, Magerl M, Maurer M, Staubach P. Omalizumab—an effective and safe treatment of therapy-resistant chronic spontaneous urticaria. *Allergy*. 2011;66:303–305.
- [11] Magerl M, Staubach P, Altrichter S, et al. Effective treatment of therapy-resistant chronic spontaneous urticaria with omalizumab. *J Allergy Clin Immunol*. 2010;126:665–666.
- [12] Vestergaard C, Deleuran M. Two cases of severe refractory chronic idiopathic urticaria treated with omalizumab. *Acta Derm Venereol*. 2010;90:443–444.
- [13] Nam YH, Kim JH, Jin HJ, et al. Effects of omalizumab treatment in patients with refractory chronic urticaria. *Allergy Asthma Immunol Res*. 2012;4:357–361.
- [14] Büyükoztürk S, Gelincik A, Demirtürk M, Kocaturk E, Colakoglu B, Dal M. Omalizumab markedly improves urticaria activity scores and quality of life scores in chronic spontaneous urticaria patients: a real life survey. *J Dermatol*. 2012;39:439–442.
- [15] Ivyanskiy I, Sand C, Thomsen SF. Omalizumab for chronic urticaria: a case series and overview of the literature. *Case Rep Dermatol*. 2012;4:19–26.
- [16] Armengot-Carbo M, Velasco-Pastor M, Rodrigo-Nicolas B, Pont-Sanjuan V, Quecedo-Estebanez E, Gimeno-Carpio E. Omalizumab in chronic urticaria: a retrospective series of 15 cases. *Dermatol Ther*. 2013;26:257–259.
- [17] Lefèvre AC, Deleuran M, Vestergaard C. A long term case series study of the effect of omalizumab on chronic spontaneous urticaria. *Ann Dermatol*. 2013;25:242–245.
- [18] Labrador-Horrillo M, Valero A, Velasco M, et al. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. *Expert Opin Biol Ther*. 2013;13:1225–1228.
- [19] Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol*. 2008;122:569–573.
- [20] Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128:567–573.
- [21] Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128:202–209.
- [22] Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924–935.
- [23] Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132:101–109.
- [24] Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol*. 2006;117:1415–1418.
- [25] Brodská P, Schmid-Grendelmeier P. Treatment of severe cold contact urticaria with omalizumab: case reports. *Case Rep Dermatol*. 2012;4:275–280.
- [26] Le Moing A, Bécourt C, Pape E, Dejobert Y, Delaporte E, Staumont-Sallé D. Effective treatment of idiopathic chronic cold urticaria with omalizumab: report of 3 cases. *J Am Acad Dermatol*. 2013;69:e99–e101.
- [27] Song CH, Stern S, Giruparajah M, Berlin N, Sussman GL. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2013;110:113–117.
- [28] Młynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy*. 2008;63:777–780.