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

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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.

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 lifetime 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 H_1-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,

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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.
[a]The 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 H_1 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 H_1 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.