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

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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 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%.4

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.5 However, more than half of patients with CSU do not respond adequately to antihistamines.6

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 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 prednisolone. Omalizumab induced a long-lasting positive response and was well tolerated without side effects.
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. 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.

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
severely do not respond to first-, second-, or third-line treat-
ments and often require systemic glucocorticoids to achieve
remission. The present study and other recently published work 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. As such, the present study adds valuable
information to the substantial and growing evidence base for
omalizumab for the treatment of urticaria.

Objectives

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term remission.

randomized, double-blinded trial in 323 patients refractory to H1
antihistamines reported clinically meaningful and statistically signif-
ican decreases in itch severity score (primary end point) and
improvements in all other studied efficacy end points. 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.

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.

Table 1

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

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

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

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 medi-
cation 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 urti-
carial 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.
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 dosages 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.

<table>
<thead>
<tr>
<th>% (n/N)</th>
<th>0–6 mo</th>
<th>6–12 mo</th>
<th>12–24 mo</th>
<th>&gt;24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>53% (18/34)</td>
<td>24% (8/34)</td>
<td>15% (5/34)</td>
<td>7% (2/34)</td>
</tr>
<tr>
<td>Toronto subgroup</td>
<td>47% (15/32)</td>
<td>29% (9/32)</td>
<td>9% (3/32)</td>
<td>15% (5/32)</td>
</tr>
<tr>
<td>Quebec City subgroup</td>
<td>62% (21/34)</td>
<td>18% (6/34)</td>
<td>21% (7/34)</td>
<td>0% (0/34)</td>
</tr>
</tbody>
</table>

*Due to rounding, rows may not add up to 100%.

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.

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.

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

% achieving remission at each time point: 17.9% 51.9% 60.0% 54.5% 71.4%

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