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ORIGINAL ARTICLE

Efficacy of omalizumab treatment for patients with chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (CSU) in Taiwan

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ABSTRACT

Background/Objectives: Accumulating evidence has shown that omalizumab is an effective and safe treatment for chronic spontaneous urticaria (CSU), but there is little information regarding the use of omalizumab to treat CSU in Taiwan. Reports on clinical experiences with using omalizumab for CSU for more than 6 months are also lacking.

Methods: A retrospective review of medical records of consecutive CSU patients receiving omalizumab treatment in the Urticaria Special Clinic of one tertiary referral center in Taiwan was conducted. We analyzed clinical features of the patients, treatment efficacy and safety, and also long-term outcomes after omalizumab treatment. An Urticaria Activity Score over 7 days (UAS7) was recorded at each visit.

Results: A total of 17 CSU patients were identified (11 females and 6 males, age range: 21–83 years) with a baseline mean UAS7 of 29.8 ± 8.9 despite antihistamine treatment. All patients were treated with at least 3 doses of monthly subcutaneous injections of omalizumab. Fifteen patients achieved a UAS7 of 6 or less after 3 doses of monthly omalizumab injections. Seven of those 15 patients received an additional 1 to 3 doses and all ended up with a UAS7 of less than 2 at the 24-week follow-up. A sustained response to maintenance treatment after 24 weeks was observed in 5 patients with individual tailoring of treatment duration and dosing interval.

Conclusion: Omalizumab is an effective and safe treatment for antihistamine refractory CSU. Maintenance therapy with individual tailoring of the treatment duration and interval is possible.

Introduction

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria (CSU), is a common disease characterized by the daily or almost daily spontaneous emergence of wheals, angioedema, or both for more than 6 weeks.[1] Due to the intolerable itching and episodic attacks of disfiguring wheals, the impact of CSU on a patient's quality of life is profound and has been reported to be similar to that experienced by patients waiting for coronary artery bypass graft surgery.[2] A nationwide cross-sectional observational study in Taiwan found that CSU causes severe psychological pressure and that most cases are not satisfactorily managed.[3] Furthermore, a case-control study identified stress and insomnia as important factors for the development and worsening of CSU, respectively.[4] Different treatment options for this rather common dermatological disease (estimated prevalence: 0.5%–5%) have already been discussed by different guidelines and consensus reports in recent years.[1,5] In the past, the pharmacological treatments of CSU mainly focused on the pathogenic role of mast cell activation. With their ability to block histamines while causing less drowsiness than other treatments, modern second generation H1-antihistamines have become the standard first-line treatment for CSU.[1,5,6] Options for second-line therapies include a trial of up to a four-fold dose of one non-sedating second generation H1 antihistamine or the addition of other antihistamines (second generation H1, first generation H1, or H2 antihistamines).[1,5] However, it has been proposed that the pathogenic role of mast cells in CSU may not only involve the downstream degranulation of histamine and proinflammatory cytokines, but also the upstream activation process. The IgE–FcεRI–mast cell axis and the presence of anti-IgE auto antibodies may increase mast cell activity without degranulation.[7] In phase II and phase III trials, omalizumab, a humanized

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monoclonal anti-IgE antibody, has been shown to be effective in the treatment of patients who remain symptomatic despite H1 antihistamine treatment, and omalizumab is also recommended as an add-on therapy to second generation H1 antihistamines.[8–11] A 300 mg subcutaneous injection every 4 weeks for 12 or 24 weeks has been shown to have a more rapid onset of action and sustainable effectiveness in comparison to lower dosing regimens.[11] Omalizumab has been licensed by the Taiwan Food and Drug Administration (TFDA) for the treatment of CSU patients with unsatisfactory responses to H1 antihistamines. Owing to the variations in clinical responses and economic considerations, the beneficial roles of personalized dosing intervals and continued treatment during extension periods have only been conceptualized in limited studies.[12,13] Herein, we report our experiences with using omalizumab for the treatment of CSU patients at a tertiary referral center in Taiwan.

Methods

Patients

We conducted a retrospective analysis of the effects of using omalizumab to treat CSU patients at the Urticaria Special Clinic of one tertiary referral center, National Taiwan University Hospital. The medical records of CSU patients who underwent omalizumab treatment between October 2013 and March 2016 were reviewed. Most of the patients were started on omalizumab therapy after exhibiting unsatisfactory responses to H1 antihistamines and persistent daily symptoms consisting of pruritus, wheals, or angioedema (Table 1). The severity of CSU for each patient was recorded using an Urticaria Activity Score over 7 days (UAS7) score at baseline and each follow-up visit. The total serum IgE levels were also documented. Omalizumab has been approved for the treatment of refractory CSU in Taiwan since December 2015. Before the approval, informed consent was obtained for any off-label use of the drug. For all the patients, three doses of 150 or 300 mg of omalizumab were injected subcutaneously every 4 weeks (i.e., at week 0, week 4, and week 8) while the patients continued receiving antihistamine therapy. After week 8, the number of and intervals between any additional injections were tailored according to the given patient's clinical response.

Assessment

Each patient was evaluated by the same dermatologist. The sum of the UAS7 at baseline and the UAS7 at the time before the administration of the next dose was recorded. The UAS is composed of a pruritus score on a scale of 0 (none) to 3 (severe) and the number of hives calculated on a scale of 0 (none), 1 (<20 wheals/24 h), 2 (20–50 wheals/24 h) to 3 (>50 hives/24 h). Treatment responses were categorized as well-controlled disease (UAS7 $\leq$ 6), complete response (UAS7 = 0), or non-response (UAS7 > 6).

Table 1 Patient's demographics (n = 17).

Age	44.6 ± 20.5
Female sex, no. (%)	11 (64.7)
Body weight (kg)	60.1 ± 10.9
Time since diagnosis of CSU (years)	5.9 ± 6.4
Mean total IgE level (IU/mL) (range)	272.6 (8.9–1510.0)
Presence of angioedema, no (%)	7 (41.2)
Mean no. of previous medications for CIU/CSU	2 ± 0.9
Previous use of corticosteroids, no. (%)	4 (23.5)
Mean baseline UAS7	29.8 ± 8.9
Mean UAS 7 at week 8	1.9 ± 4.0
Mean UAS 7 at week 12	1.5 ± 3.6

Statistical analyses

Demographic data were analyzed by descriptive statistics. Measurement data for each group were shown in terms of mean ± SD. Statistical comparisons between the groups were made using the Student's *t*-test (Excel 2007, Microsoft Corp., Redmond, WA, USA). Statistical significance was defined as $P < 0.05$.

Results

Seventeen CSU patients with a UAS7 of more than 16 despite receiving different H1 antihistamines were identified. The demographic data of these patients are summarized in Table 1. The mean duration of CSU was 5.9 years (range: 2 months to 20 years). The treatment regimen and response are shown in Table 2. Four patients had been treated with different doses of systemic corticosteroids. The average baseline UAS7 was 29.8 ± 8.9. All the patients received 3 initial subcutaneous doses of 150 or 300 mg of omalizumab at an interval of every 4 weeks. For every patient, a significant reduction of UAS7 was found over time (Fig. 1). The clinical efficacy of the treatment in terms of the urticaria disease activity during the treatment period was demonstrated by increased proportions of well-controlled disease (UAS7 $\leq$ 6) and complete response (UAS7 = 0) (Fig. 2). At week 12, 88.2% patients had a well-controlled disease and 76.5% patients had achieved a complete response. Disease flare-ups while receiving omalizumab therapy were observed in 2 patients due to the patient's discontinuation of all baseline antihistamines. One of those patients (patient No. 6) then achieved well-controlled status by adding on levocetirizine and buclizine while continuing the omalizumab treatment and the other (patient No. 7) was lost to follow-up. The response parameters, including UAS7 at week 12 and the total number of injections, did not correlate with the IgE levels or the presence of angioedema (statistical data now shown).

Individualized treatment duration, interval, and dose

Five patients received omalizumab for maintenance therapy after 6 doses of omalizumab over 24 weeks and reached a UAS7 of 6 or less. Satisfactory maintenance effects were achieved by tailoring omalizumab treatment to each patient's individual condition.

Of the 5 patients who received extended treatment of a duration ranging from 16 to 78 weeks beyond week 24, four obtained and maintained a complete response, while the fifth achieved the well-controlled disease status (Table 3). With regard to extended dosing interval, one patient maintained a complete response on 150 mg doses of omalizumab with dose intervals tapered from every 4 weeks to every 12 weeks; one patient had a well-controlled disease, and the remaining two patients had a complete response on 300 mg doses of omalizumab at intervals of 4–8 weeks.

Among three patients received antihistamine only as maintenance treatment, one remained in complete remission and patient No. 5 and No. 17 experienced flares 8 and 9 weeks respectively after the end of omalizumab treatment.

Safety

During the treatment period, no severe adverse events such as death or anaphylactic shock were reported. Only one patient experienced nausea and another had an injection-site reaction presenting as a painful induration for 1 day after the first injection. Neither of those patients had a recurrence of similar side effects after the first injection.

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