

ORIGINAL ARTICLE

Does omalizumab modify a course of recalcitrant chronic spontaneous urticaria?: A retrospective study in Asian patients

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ABSTRACT

Omalizumab has been approved for the treatment of recalcitrant chronic spontaneous urticaria (CSU). However, it remains unanswered whether omalizumab modifies a CSU course. We aimed to study a course of CSU after omalizumab treatment in an Asian population. Medical records of recalcitrant CSU patients who attended Siriraj Hospital between 2013 and 2017 were reviewed. All patients receiving omalizumab treatment were followed after the first injection for at least 1 year. Of 15 patients receiving omalizumab treatment, 11 patients (73.3%) responded well to 150 mg while the rest required 300 mg. The median follow-up period was 18 months (range, 13.5–25.3). Three patterns of response were proposed and measured: excellent (disease remission over than 6 months) was found in 20%; good (injection interval extended longer than 6 months) was found in 27%; and modest (frequently required injections) was found in 53%. The mean duration of complete remission was 33 weeks (range, 26–38). Two-thirds of patients had disease relapse and required omalizumab injections to control symptoms. The other third did not show relapses for at least 69 weeks of the follow-up period. After 1 year of treatment, Kaplan–Meier curves estimated that a higher percentage (86.7%) of recalcitrant CSU patients receiving omalizumab treatment would be free of symptoms (weekly Urticaria Activity Score = 0) without prednisolone and/or cyclosporin as compared with 42% of patients not receiving omalizumab treatment. In conclusion, patients seem to be easily and safely manageable with omalizumab. Prednisolone and cyclosporin could be discontinued in all patients. Further studies are needed to conclude whether omalizumab can exactly modify CSU.

Key words: modify chronic spontaneous urticaria course, omalizumab, recalcitrant chronic spontaneous urticaria, treatment, weekly Urticaria Activity Score.

INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by an occurrence of itchy wheals and flares for a consecutive 6 weeks or more with or without identified causes.¹ Autoimmunity is proposed to be one of the most frequent causes of CSU. For type I autoimmunity, type I autoantigens or autoallergens such as immunoglobulin (Ig)E anti-dsDNA and IgE anti-thyroperoxidase can activate mast cells and basophils by cross-linking IgE autoantibodies (AAb). For type II autoimmunity, IgG AAb can activate mast cells and basophils by binding to IgE or to FcεRI, which may then involve C5a and CD88/C5aR receptor.² Many studies reported that omalizumab (monoclonal anti-IgE antibodies) is very effective in the treatment of refractory CSU.^{3–5} Recent proposed mechanisms of action of omalizumab in CSU patients with type I autoimmunity is that omalizumab rapidly binds free IgE AAb and forms omalizumab–IgE immune complexes. These

complexes bind autoallergens and reduce mast cell activation, causing rapid response to treatment within 1 week in more than half of the patients. For type II autoimmunity, omalizumab causes downregulation of free IgE, resulting in downregulation of FcεRI on mast cell surfaces, which makes them less susceptible to activation by IgG anti-IgE and IgG anti-FcεRI. These patients respond more slowly to omalizumab treatment.² Gericke *et al.* suggested that patients with positive basophil histamine release test or positive autologous serum skin test tended to have slow response to omalizumab.⁶

Currently, an important issue of whether omalizumab can have a role in modifying a course of CSU remains unanswered. This study was aimed to determine the disease course of recalcitrant CSU in patients who received omalizumab treatment in terms of duration of treatment until disease remission, duration of remission and relapse rate after drug discontinuation in an Asian population.

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METHODS

This study was ethically approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (approval no. Si656/2016). Medical records of CSU patients who visited the Skin Allergy Clinic, Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, during March 2013 to February 2017 were retrospectively reviewed. Informed consent was written and signed in all cases. Patients with omalizumab treatment who were followed after the first injection for at least 1 year were enrolled in the study.

A stepwise approach to initiate omalizumab in our recalcitrant CSU patients were followed according to the recommendations of the Dermatological Society, the Allergy, Asthma and Immunology Association, and the Pediatric Dermatological Society of Thailand.⁷ Due to its relatively high cost, a step-ladder treatment should be performed as follows: (i) a standard dose of non-sedating H₁-antihistamines for 2–4 weeks; (ii) up to fourfold doses of modern second-generation antihistamines for 2–4 weeks; (iii) combination with H₂-antihistamines or leukotriene receptor antagonists and/or short course of oral corticosteroids at a dose of 10 mg/day or less for less than 4 weeks in patients who do not have contraindications; and (iv) cyclosporin of 3 mg/kg per day may be added in patients who do not have contraindications. In patients with corticosteroids or cyclosporin dependence, corticosteroids or cyclosporin side effects, and weekly Urticaria Activity Score (UAS7) scores of 16 or more after this stepwise approach, omalizumab should then be added as an add-on therapy. After a 150-mg omalizumab injection, patients with a significant improvement (reductions in UAS7 scores of $\geq 30\%$) can continue omalizumab injection with the same dose by an interval of 4 weeks. Doubling the dose of omalizumab (300 mg) should be used in patients with a reduction in UAS7 less than 30%. In patients who have responded well, the injection interval of omalizumab will be extended and then discontinued if it is possible.

The UAS7 score and medication score were used to assess disease severity.^{8,9} The UAS7 consists of the daily number of wheals (range, 0 [none] to 3 [severe]) and daily pruritus severity (range, 0 [none] to 3 [severe]) for 7 days consecutively, with a maximum sum score of 42. Disease severities were categorized as follows: complete response (0), well controlled (1–6), mild (7–15), moderate (16–27) and severe (28–42).⁸ All patients were asked to record UAS7 by themselves for 1 week prior to each follow up. The medication score is a quantitative severity measurement score in CSU. The score is calculated based on the sum of total drug use in CSU. Each drug is classified to have a score as follows: antihistamines (2 points, regular dose; 8 points, up to fourfold dose), oral corticosteroids (<11 mg, 5 points; 11–25 mg, 10 points; >25 mg, 15 points), cyclosporin (3 mg/kg, 8 points), hydroxychloroquine (6 points) and leukotriene receptor antagonist (2 points).⁹

It is assumed that total serum clearance of a drug from the body should be equal to fivefold of the drug half-life.¹⁰ Range of serum terminal half-life of omalizumab was reported to be between 18 and 26 days.^{11–15} Based on maximal terminal half-

life of omalizumab of 26 days, it should be eliminated from the body within 130 days (5 months) after the last injection.¹² In our study, complete remission was defined as UAS7 of 0 without any medications for more than 6 months. For disease relapse, patients who had recurrence of CSU after a 6-month period of complete remission were considered to have had a disease relapse. Kaplan–Meier analysis was performed to investigate the probability of achieving: (i) a reduction in UAS7 of 30% or more from baseline (significant improvement); and (ii) UAS7 of 0 without prednisolone and/or cyclosporin in the omalizumab-treatment group and control group.¹⁶ To avoid selection bias, patients in the control group of this observational retrospective study were recruited in the same period of time as the patients in the study group. We recruited all recalcitrant CSU patients who had the same severity as patients in the study group. All patients in the control group had at least the first three-step-ladder approach but omalizumab was not affordable due to financial problem or personal reasons.

RESULTS

This study included a total of 15 recalcitrant CSU patients who underwent omalizumab treatment (eight women, seven men) with a mean age of 42.9 ± 14.2 years. The median follow-up period was 18.9 ± 3.8 months with a range between 13.5 and 25.3 months. Of 15 patients, 11 (73.3%) responded well to 150 mg while four patients (26.7%) required up-dosing to 300 mg omalizumab. Table 1 shows disease activity, treatment duration and duration of remission of patients receiving 150 mg omalizumab injection. All patients had significant improvement ($\geq 30\%$ reductions in UAS7) after 150-mg omalizumab treatment.

Three patients (1–3) had complete remission (free of CSU symptoms without omalizumab and conventional therapies for >6 months) with the mean duration of 33 weeks. Mean duration of omalizumab treatment before complete remission was 23.7 weeks (range, 15–34). Patients 1 and 2 had complete remission for 26 and 38 weeks, respectively, and then experienced disease relapse. During the flare-up period, their symptoms were uncontrolled despite fourfold non-sedating H₁-antihistamine. Omalizumab with the same dose was re-initiated which showed similar good response. In patient 1, CSU symptoms could be controlled with one injection of omalizumab. Only antihistamines were required during the follow-up period (31 weeks) after re-treatment.

Three patients (4–6) remained asymptomatic for a long duration (range, 39–53 weeks) by using antihistamines during omalizumab extension. Five patients (7–11) had to receive omalizumab injection every 4 up to 12 weeks together with antihistamine intake. After omalizumab administration, all patients could discontinue cyclosporin and systemic corticosteroids.

Table 2 demonstrates disease activity, treatment duration and duration of remission of patients receiving 300-mg omalizumab injection. Patient 13 had both CSU and cold urticaria while patient 15 had CSU, angioedema and asthma. No patients in this group had complete remission and only one

Table 1. Disease activity, treatment duration, duration of remission of patients receiving 150-mg omalizumab injection

Case no.	Sex	Age (yrs)	CU duration before omalizumab (years)	Omalizumab injection																				Remission
				Baseline	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	
1	F	67	3	Dose (mg) UAS7 = 10 Med = 25 Week	150 [†] 0 13 0	150 [†] 0 2 4	150 [†] 0 0 8	150 [†] 0 0 15	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	150 [†] 0 0 150 [†]	Yes then relapsed
2	F	25	2	Dose (mg) UAS7 = 27 Med = 20 Week	150 [†] 0 12 0	150 [†] 0 3 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	72 (present) Yes then relapsed
3	F	19	3	Dose (mg) UAS7 = 23 Med = 22 Week	150 [†] 0 12 0	150 [†] 0 4 8	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	Yes
4	M	56	5.5	Dose (mg) UAS7 = 16 Med = 21 Week	150 [†] 0 16 0	150 [†] 0 12 8	150 [†] 0 8 12	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	No
5	M	24	4.5	Dose (mg) UAS7 = 7 Med = 20 Week	150 [†] 0 10 0	150 [†] 0 3 4	150 [†] 0 6 8	150 [†] 0 4 13	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	No
6	F	43	7.5	Dose (mg) UAS7 = 39 Med = 25 Week	150 [†] 0 13 0	150 [†] 0 2 4	150 [†] 0 2 8	150 [†] 0 4 13	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	No
7	M	42	8	Dose (mg) UAS7 = 18 Med = 30 Week	150 [†] 0 22 0	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	150 [†] 0 12 8	No
8	F	41	2	Dose (mg) UAS7 = 4 Med = 31 Week	150 [†] 0 16 0	150 [†] 0 2 0	150 [†] 0 12 8	150 [†] 0 8 12	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	No
9	F	42	2.5	Dose (mg) UAS7 = 42 Med = 16 Week	150 [†] 8 10 10	150 [†] 2 14 9	150 [†] 150 10 10	150 [†] 150 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	150 [†] 150 [†] 10 10	No
10	M	26	5.6	Dose (mg) UAS7 = 19 Med = 23 Week	150 [†] 12 4 8	150 [†] 4 8 8	150 [†] 150 150 150	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	No
11	F	62	10.5	Dose (mg) UAS7 = 29 Med = 31 Week	150 [†] 1 8 2	150 [†] 14 0 2	150 [†] 150 [†] 14 0	150 [†] 0 2 4	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	150 [†] 0 0 0	No

[†]Extended duration of injection for more than 4 weeks. CU, chronic urticaria; disease relapse, recurrence of CSU after 6 months of remission; Med, medication score; UAS7, Urticaria Activity Score for consecutive 7 days after the treatment; remission, UAS7 of 0 without any medications for more than 6 months.

[Extended duration of injection for more than 4 weeks. CU, chronic urticaria; disease relapse, recurrence of CSU after a 6 months of remission; Med, medication score; UAS7, Urticaria Activity Score for consecutive 7 days after the treatment remission UAS7 of 0 without any medications for more than 6 months.

[illegible]

Figure 1. (a) In the omalizumab-treatment group, 66.7% and 100% of recalcitrant chronic spontaneous patients had a significant improvement without prednisolone and/or cyclosporin at weeks 1 and 8, respectively. In the control group, 0% and 27% of patients achieved a significant improvement at weeks 1 and 8, respectively. (b) After initiating the treatment for 1 year, 86.7% of recalcitrant chronic spontaneous urticaria (CSU) patients who underwent omalizumab treatment and 42% of those who did not undergo omalizumab treatment (control group) were free of CSU symptoms (Urticaria Activity Score of 7 days [UAS7] = 0) without prednisolone and/or cyclosporin.

The control group included 30 patients (22 women, eight men) who had had at least the first of the three-step-ladder approach without omalizumab treatment. The mean age of the control group was 43.4 ± 16.9 years. Kaplan–Meier analysis demonstrated a probability of recalcitrant CSU patients achieving: (i) a significant improvement (a reduction in UAS7 of $\geq 30\%$); and (ii) symptom-free state (UAS7 = 0) after the

Table 3. Summary of reported long-term studies of omalizumab treatment of chronic urticaria

Study	Diagnosis	n	Study duration period (months)	Omalizumab dose	Definition of response	Response rate, n (%)	Remission without any medication ≥ 6 months, n (%)	Duration until remission	Relapsed cases, n (%)	Duration until relapse
Retrospective reviews										
Ghazianfar <i>et al.</i> ¹⁸ (2016)	CSU or CINDU	154 (CSU = 137, CINDU = 17)	12	70/154 (45.5%), initial dose of 150 mg q 2 wk; 5% changed to 150 mg q 4 wk; 11% changed to 300 mg q 2–4 wk; 84/154 (55%), initial dose of 300 mg q 4 wk; 6% changed to 150 mg q 2–4 wk or 300 mg q 6 wk; 7% changed to 300 mg q 2–3 wk	CR or almost CR; $\geq 90\%$ reduction of symptoms PR; 30–89% reduction of symptoms NR or limited response; $<30\%$ reduction of symptoms Evaluation after 3–6 months of treatment	CSU, 92/137 (67%), CR or almost CR; 31/137 (22%), PR; 14/137 (10%); NR or limited response; 22/137 (16.1%), symptomatic remission CINDU, 9/17 (53%), CR or almost CR, 2/17 (12%), symptomatic remission	None	N/A	14/24 (58%) (CSU and CINDU)	N/A
Ensina <i>et al.</i> ¹⁹ (2015)	Recalcitrant CSU	9	23 (mean) (range, 12–61)	2/9 (22%), initial dose of 150 mg q 4 wk; 1/2 (50%) changed to 150 mg q 6 wk; 1/2 (50%) changed to 300 mg q 4 wk	CR; total absence of symptoms PR; improvement on urticaria but still with symptoms or additionally taking AH	1/2 (50%), CR; 1/2 (50%), PR	None	N/A	N/A	N/A
Har <i>et al.</i> ²⁴ (2015)	Recalcitrant CU	10	27 (median) (range 17–112)	Initial dose 150 q 4 wk; 450 mg q 2 wk	– CR; total absence of symptoms – PR; improvement on urticaria CR; UAS7 = 0	8/10 (80%), CR; 7/8 (88%), CR after the 1st dose; 1/8 (12%), CR after the 3rd dose	None	N/A	N/A	N/A
Silva <i>et al.</i> ²⁰ (2015)	Recalcitrant CSU	7	35 (median) (range 29–40)	150–300 mg q 2–6 wk	CR; UAS7 = 0	7/7 (100%); 4/7 (57%), CR after the 1st dose; 1/7 (14%), CR after the 2nd dose; 2/7 (28%), CR after the 4th dose	None	N/A	N/A	N/A
Metz <i>et al.</i> ¹⁷ (2014)	CSU or CINDU	25 (15 CSU)	N/A	150–600 mg q 2–4 wk	CR; UAS7 decrease $\geq 90\%$	25/25 (100%); all patients had complete symptom control without the requirement of any other drugs used after their first omalizumab injection	1/25 (4%)	N/A	23/25 (92%) 2/25 (8%)	2–8 wk 4 and 7 months
Song <i>et al.</i> ²¹ (2013)	Severe CSU	16	Range, 9–24	150 mg q 4–8 wk	CR; UAS7 = 0	10/16 (62.5%) after 1st dose; 2/16 (12.5%) after 3rd dose; 1/16 (6.25%) after 5th dose; 1/16 (6.25%) after 6th dose	4/16 (25%)	N/A	N/A	N/A
Case series										
Florino <i>et al.</i> ²² (2014)	Severe chronic urticaria	2	21	1/2 (50%), 300 mg q 4 wk with AH for 9 months then 450 mg q 4 wk enabled discontinuation of AH	CR; UAS7 = 0	1/1 (100%)	None	N/A	N/A	N/A
Lefèvre <i>et al.</i> ²³ (2013)	CSU	15	48 15.53 (median) (range, 2–37)	1/2 (50%), 150 mg q 4 wk 8/14 (57%), 150 mg q 4 wk; 2/14 (14%), 300 mg q 2 wk; 4/14 (28%), 300 mg q 4 wk	N/A	1/1 (100%) Average DLQI decrease from 13.4 to 3.8 ($P < 0.001$) after 1st month; UAS7 decrease from 31.1 to 8.0 ($P < 0.001$) over the 1st month	None	N/A	N/A	N/A

AH, antihistamine; CINDU, chronic inducible urticaria; CR, complete response; CSU, chronic spontaneous urticaria; DLQI, Dermatological Quality of Life Index; N/A, not available; NR, no response; PR, partial response; wk, week; UAS7, Urticaria Activity Score of 7 days.

initiation of the treatment. In the omalizumab-treatment group, 66.7% and 100% of patients had a significant improvement without prednisolone and/or cyclosporin at weeks 1 and 8, respectively. In the control group, 0% and 27% of patients achieved a significant improvement at weeks 1 and 8, respectively (Fig. 1a). After initiating the treatment for 1 year, 86.7% who underwent omalizumab treatment and 42% of the patients who did not undergo omalizumab treatment were free of CSU symptoms (UAS7 = 0) without prednisolone and/or cyclosporin (Fig. 1b).

DISCUSSION

Reported long-term studies of omalizumab treatment of chronic urticaria are summarized in Table 3.^{17–24} Complete response or complete control of CSU symptoms were mentioned in most studies but information on other treatments during response was inexact. To our knowledge, there is no consensus regarding the definition of complete remission after omalizumab treatment. Patients who do not have CSU symptoms without any medications for longer than 6 months were defined as having disease remission in our study. Metz *et al.*¹⁷ studied 25 (CSU and chronic inducible urticaria) patients by using omalizumab 150–600 mg every 2–4 weeks. All patients had complete control of their symptoms (defined as $\geq 90\%$ improvement) without the requirement of any other drug use after their first omalizumab injection. All patients showed relapse of disease within 2 weeks to 7 months. After the first dose of omalizumab re-initiation, rapid and complete responses were reported in all patients. However, our study focused on the disease course of recalcitrant CSU patients who received omalizumab in terms of duration of treatment until disease remission, duration of remission and relapse rate after drug discontinuation.

Kolkhir *et al.*² classified the initial response of CSU patients to omalizumab as rapid and slow responses. In terms of duration of treatment until disease remission, duration of remission and relapse rate after drug discontinuation, we classified our patients into three groups as follows:

- 1 Excellent response (20%): these patients had disease remission (UAS7 of 0 without any medications for >6 months). In this group (three patients of the 150-mg group), remission occurred after 15–34 weeks of omalizumab injections despite previous prednisolone and cyclosporin intake. Compared with the natural course of CSU, it seemed that omalizumab may help physicians to control recalcitrant CSU more easily without medications with potential side-effects. It should be noted here that two of three patients had disease relapse. However, their disease relapse could be easily controlled with the same dose and only a few injections of omalizumab.
- 2 Good response (27%): injection interval of omalizumab could be extended longer than 6 months. Our four patients (4–6 of the 150-mg group and patient 12 of the 300-mg group), injection interval could be extended up to more than 1 year (mean, 43.7 weeks; range, 39–53). This group did not have disease remission because antihistamines were needed to control their CSU symptoms but they required omalizumab

injections less frequently. Previous prednisolone and cyclosporin could be discontinued.

- 3 Modest response (53%): omalizumab injections were more frequently required than the second group to control their symptoms. Our eight patients (7–11 of the 150-mg group and patients 13–15 of the 300-mg group) required omalizumab injections every 4–12 weeks to control their symptoms. Even though antihistamines were needed in all patients, prednisolone and cyclosporin could be discontinued.

Before the era of omalizumab, clearing of CSU symptoms after 1 and 5 years was reported to be 20–80%, and 84–96%, respectively.^{25–30} Kozel *et al.*²⁶ reported the natural course of physical and chronic urticaria and angioedema in 220 patients. Among their 78 patients with CSU, 47.4% were free of symptoms after 1 year. Of those with urticaria only, angioedema only, and both urticaria and angioedema, 38.5%, 20% and 59.5% were free of symptoms after 1 year, respectively. Kulthanan *et al.*²⁹ reported that 34.5% and 84% of Thai CSU patients were free of symptoms without any medications after 1 and 5 years, respectively, from the onset of disease. Hiragun *et al.*³⁰ reported prognosis of 117 CSU patients whose disease could not be controlled by a standard dose of antihistamines. Disease remission was defined as no symptom for 1 month or more without any medications. The estimated remission rates in Hiragun *et al.*'s study at 1, 2 and 5 years from the first visit were 11.5%, 13.9% and 27.7%, respectively. Our Kaplan–Meier curve showed that an increased percentage of recalcitrant CSU patients who underwent omalizumab treatment achieved a significant improvement (a reduction in UAS7 of $\geq 30\%$) within 1 and 8 weeks of treatment as compared with those who did not undergo omalizumab treatment. Similarly, a higher percentage of recalcitrant CSU patients who underwent omalizumab treatment were free of CSU symptoms (UAS7 = 0) without prednisolone and/or cyclosporin after 1 year as compared with those of the control group. It should be noted here that we had a small number of cases and limited follow-up period.

In conclusion, recalcitrant CSU patients seem to be easily manageable with omalizumab. Prednisolone and cyclosporin could be discontinued in all patients. Further studies with a larger number of patients and longer follow-up period are needed to conclude whether omalizumab can exactly modify the natural course of CSU.

CONFLICT OF INTEREST: Professor Kanokvalai Kulthanan was an educational lecturer for Novartis. The other authors declare no conflicts of interest.

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