

Report

The treatment outcomes and dose de-escalation of desloratadine up-dosing in chronic spontaneous urticaria

Charoen Choonhakarn, MD, Suteeraporn Chaowattanapanit, MD, and
Narachai Julanon, MD

Division of Dermatology, Department of
Medicine, Faculty of Medicine, Srinagarind
Hospital Medical School, Khon Kaen
University, Khon Kaen, Thailand

Correspondence

Charoen Choonhakarn, MD
Division of Dermatology
Department of Medicine
Faculty of Medicine
Srinagarind Hospital Medical School
Khon Kaen University
Khon Kaen 40002
Thailand
E-mail: c_choonhakarn@yahoo.com

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Abstract

Background An increase in dosages up to fourfold of second generation antihistamines is recommended for recalcitrant chronic spontaneous urticaria (CSU). No regimen guidelines about dose de-escalation, however, are mentioned once the disease is controlled.

Objective To demonstrate the treatment outcomes and dose reduction in desloratadine assessed using the urticarial activity score over 7 consecutive days.

Methods Medical records of all patients with CSU treated with desloratadine were collected retrospectively during a period from January 2010 to December 2013.

Results Sixty-seven (94.4%) patients had remission of the disease with variable doses of desloratadine. The patients who had CSU concomitant with antithyroid antibodies or high erythrocyte sedimentation rates had a greater tendency not to respond to the standard dose. Once the disease was completely controlled, 67 patients finished the treatment, but 63 (94%) patients had recurrent symptoms. Sixty-three patients took the same dose that induced the response for a further 4 weeks before stopping or reducing the dose, 41/63 (65.1%), however developed urticaria again. Forty-one patients took the same dose for a further 8 weeks; only 2/41 (4.9%) patients developed the rash again. The mean follow-up period after the disease was controlled was 7.5 months.

Conclusion Most patients need higher than the standard doses to obtain remission. Once the disease is completely controlled, however, maintenance of the same dosage for at least 8 weeks before dose reduction is suggested in order to avoid recurrence of the symptoms.

Introduction

Chronic urticaria (CU) may seem as a non-life-threatening disease, but in reality, it is severe and often debilitating especially due to the itch. It may lead to the loss of both the social life and work of the patients. Chronic spontaneous urticaria (CSU) is characterized by the spontaneous appearance of widespread edematous, pruritic wheals surrounded by a red flare that lasts ≥ 6 weeks and can recur.^{1,2} CSU is a challenge in regard to treatment. Current international guidelines propose that second-generation non-sedating antihistamines constitute the first line of treatment for urticaria, whether acute or chronic. The European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA²LEN/EDF/WAO)² guidelines state that before considering an alternative treatment, a trial of second-generation antihistamines at doses up to four times indicated is warranted for patients who do not respond to standard doses when the potential benefits outweigh any risks. In addition, increased antihistamine doses improve patient

quality of life without increasing somnolence. Once this disease is completely controlled, however, the optimal method for reducing the dose of antihistamine has not been determined.

Desloratadine is a non-sedating, second-generation H1-antihistamine. Overall, the quality of evidence is high for desloratadine being safe and effective in CU, leading to strong recommendations for its use.³⁻¹⁰ The purpose of this study is to present retrospective data obtained from patients who were treated for CSU with desloratadine, especially those who were treated with dosages above the standard dose range. The follow-up responses were monitored after the disease was completely controlled.

Methods**Study participants**

All medical records of outpatients of Srinagarind Hospital Medical School who were aged 18 years or over and were diagnosed as CSU patients during a period of 4 years from January 2010 to December 2013 were retrospectively reviewed.

The diagnosis of CSU was based on clinical features and laboratory investigations.

Data collection

Data obtained included baseline characteristics of the patients including age, sex, the number of visits, the total treatment time in the skin clinic, and the effect of a given dose of desloratadine. Paraclinical measurements such as complete blood count, thyroid antibodies, antinuclear antibodies (ANA) and hepatitis serology including viral hepatitis B and C, and erythrocyte sedimentation rate (ESR) were also done. The effect of the treatment was evaluated using the urticarial activity score ranging from 0 to 42 over 7 consecutive days (UAS7).¹¹ All patients had to complete the questionnaire of UAS7 for the past 7 days before every visit. This timeframe between the visit and change in the treatment is suggested by the EAACI/GA²LEN/EDF/WAO guidelines.² Patients who had no urticarial lesions and no pruritus (UAS7 = 0) for the last 7 days of treatment were considered to be symptom free and therefore had a complete response. The conventional daily dose of 5 mg was initially administered to every patient. The remaining still symptomatic patients were given an up-dosing every 2–4 weeks to 10, 15, and 20 mg/day. The follow-up period after the treatment response was evaluated. Dose de-escalation, 5 mg every visit, was performed in patients who received desloratadine above the normal dose and whose responses were graded as complete remission.

Statistical analysis

Demographic data variables were collected. All variables used descriptive statistics, presentations in percentage, mean, and standard deviations (SD). If the distribution of these data was not a normal distribution, then medians and interquartile ranges (IQR) were used instead. All the data analyses were carried out using STATA version 10.0 (StataCorp, College Station, TX, USA). Ethics approval was provided by the ethics committee for human research of the Faculty of Medicine, Khon Kaen University, respecting of the Helsinki Declaration.

Results

Medical records of 85 patients who were diagnosed with CSU and treated with desloratadine were reviewed. Fourteen patients were excluded because medical records were not complete for proper assessment. Fifty-nine (83.1%) of the 71 patients were female, and 12 (16.9%) were male. Ages ranged from 22 to 64 years (mean 43.3 years). The mean duration of the disease before coming to this hospital was 3.7 months (1.5–19 months). Mean initial UAS7 score was 28.6 (12–42). Eighteen patients (25.1%) had angioedema concurrent with CSU. Thirteen patients (18.3%) had increased levels of antithyroid antibodies, antithyroglobulin and thyroperoxidase, but no patients had abnormalities of the thyroid function tests. Two patients (2.8%)

had hepatitis B viral infection without transaminitis. Ten patients (14.1%) had an antinuclear antibody (ANA) test of more than 1 : 80, but no other criteria for systemic lupus erythematosus were found. The erythrocyte sedimentation rate was increased above the normal limit of 20 mm/h in 12 patients (16.9%), mean 28 mm/h, range 22–48. Atherosclerotic-related diseases, which included diabetes, hypertension, and dyslipidemia, were the most common comorbid diseases (Table 1). Previous treatments were first generation antihistamines (42 patients, 59.2%), second generation antihistamines including loratadine and cetirizine (39 patients, 54.9%), prednisolone (12 patients, 16.9%), and calamine lotion (6 patients, 8.5%). Most patients (66 patients, 93%) took antihistamines irregularly only when symptoms occurred.

Sixty-seven patients had remission of the disease with variable doses of desloratadine. Twelve patients (16.9%) at 5 mg, 27 (38.0%) at 10 mg, 15 (21.1%) at 15 mg, and 13 (18.3%) at 20 mg of desloratadine responded completely. Four (5.6%) patients continued to have symptoms even after taking four times of the 5 mg standard dose (Fig. 1). Once the disease was completely controlled (UAS7 = 0), 67 patients stopped or reduced the dose, 5 mg every 2–4 weeks, immediately, but the symptoms recurred in 63 (94%) patients, mostly within 1–2 weeks. A satisfactory response was, however, noted again after readministering the same dose that was previously given. Sixty-three patients who had recurrent symptoms took desloratadine at the dose that induced remission for a further

Table 1 Baseline characteristics of patients with chronic spontaneous urticaria

Variables, N = 67	N
Female, n (%)	59 (83.1)
Age; range in years (mean)	22–64 (43.3)
Initial UAS7; range (mean)	12–42 (28.6)
Comorbid diseases, n (%)	
Hypertension	9 (13.4)
Dyslipidemia	5 (7.5)
Diabetes mellitus	5 (7.5)
HIV infection	2 (3.0)
Obstructive sleep apnea	1 (1.5)
Allergic rhinitis	1 (1.5)
Malignancy	1 (1.5)
Psychiatric disease	1 (1.5)
Tuberculosis	1 (1.5)
Laboratory abnormalities, n (%)	
Thyroid antibodies	13 (18.3)
ESR >20 mm/h	12 (16.9)
ANA titer >1 : 80	10 (14.1)
HBsAg positive	2 (2.8)
Follow-up duration after the disease completely controlled; range in months (mean)	6–10.5 (7.5)

UAS7, urticarial activity score over 7 consecutive days; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody.

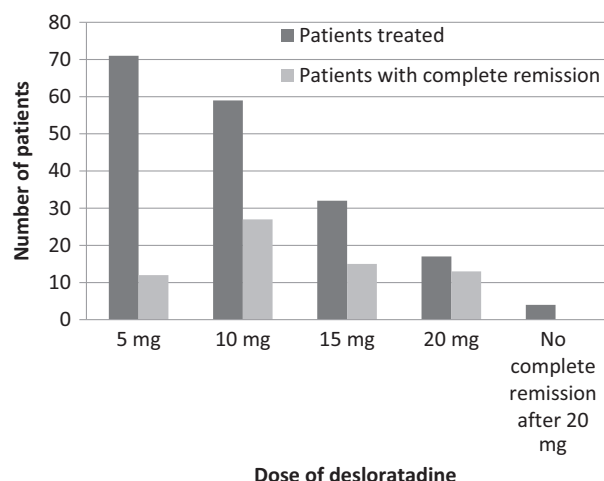


Figure 1 Treatment outcome with desloratadine's dose escalation

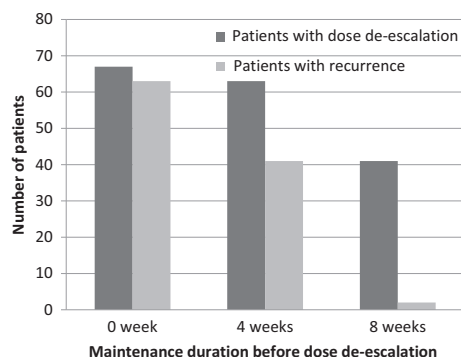


Figure 2 Treatment response of dose reduction with variable maintenance duration

4 weeks before stopping or reducing the dose, however 41/63 (65.1%) patients developed the rash again. The rash occurred in 30 patients within 1–2 weeks after stopping the medication, and in 11 patients, it occurred within 3–4 weeks. Again, the patients responded completely after readministering the previously effective dose. Forty-one patients took the same dose for a further 8-week period before stopping or dose de-escalation; only 2/41 (4.9%) patients developed the rash again after a 3- and 5-week follow-up period (Fig. 2). The mean follow-up duration after the disease was completely controlled was 7.5 months (6–10.5 months). Of the four patients who did not get remission after receiving four times the standard dose, one patient responded well after combining desloratadine with montelukast at 10 mg/day, two had symptoms clear after additional treatment with 150 mg/day of cyclosporine, and one needed omalizumab for controlling the disease. The patients who had CSU concomitant with antithyroid antibodies or high ESR more than 20 mm/h had a greater tendency not to respond to the standard dose of desloratadine. No statistically significant

Table 2 Frequency and factors associated with the lack of response to a standard dose of desloratadine

Factors	Lack of response/response, n	OR (95% CI)	P value
Angioedema			
Present	4/14	1.5 (0.27–6.53)	0.7205
Not present	8/41		
Antithyroid antibodies			
Positive	7/6	11.4 (2.87–46.0)	0.0002
Negative	5/49		
ANA			
>1 : 80	4/6	4.1 (0.67–21.68)	0.0703
Negative	8/49		
ESR			
>20 mm/h	5/7	4.9 (1.28–19.04)	0.0178
≤20 mm/h	7/48		

ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; OR, odds ratio; CI, confidence interval.

differences were found between the lack of response to a standard dose of desloratadine and angioedema or ANA titer more than 1 : 80 (Table 2).

A concern with increased doses of antihistamines is somnolence. Only two patients from this study who received desloratadine above the standard dose complained of mild drowsiness which did not disturb their work, and they were able to continue this medication. A complete blood count, blood urea, creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were performed in all patients who received antihistamine above the standard dose. One patient had mild transaminitis (ALT 51/AST 44 IU/l), but this patient also received simvastatin. When simvastatin was stopped, ALT returned to normal while the patient still took the antihistamine. One patient developed leukopenia (3140 mm^3), but this was reversed when the medication stopped. Because of the mild leukopenia, the patient was rechallenged with desloratadine once the white blood cell count returned to normal, and no abnormality of the WBC count was observed thereafter.

Discussion

Desloratadine, the principal active metabolite of loratadine, is an active nonsedating, H₁-receptor antagonist. It has approximately 10–20 times the H₁ receptor-binding potency of its parent compound *in vitro* and 50 times greater affinity for H₁ receptors than for H₂ receptors. Up to 63% of desloratadine remained bound to H₁ receptors 6 hours after administration. Prolonged H₁-receptor occupancy may explain the long duration of action. For an anti-inflammatory effect, desloratadine has been found to diminish histamine-induced activation of endothelial cells and inhibits the secretion of endothelial cytokines. It dose-dependently inhibits both IgE- and non-IgE-induced

leukocyte histamine release from basophils.¹² One study found that of the five antihistamines studied, desloratadine was the most potent inhibitor of NF- κ B activity, a regulator of gene expression in response to allergic inflammation.¹⁰

The EAACI/GA²LEN/EDF/WAO guidelines for the management of CU recommends aiming for complete symptom control by continuously administering modern second generation H1-antihistamines as first-line treatment. The second step of guidelines recommends preferably increasing the dose up to a fourfold level of modern second generation H1-antihistamines instead of combining different H1-antihistamines for patients with refractory CU.² If the patients do not go into remission, a combination with omalizumab, cyclosporine, or montelukast is the third step. This is different from the AAAAI/ACAAI Joint Task Force,¹³ recently updated in 2014, suggesting that another second-generation antihistamine, H2-antagonist, leukotriene-modifying agent or first-generation antihistamine taken at bedtime could also be considered as the second step. If no response is observed, dose advancement of sedating first-generation antihistamine as tolerated is the next step before prescribing omalizumab or cyclosporine. Recent studies reported that sedating antihistamines at bedtime combined with nonsedating antihistamines did not improve treatment efficacy in CSU. In fact, that combination taken at bedtime appeared to enhance adverse effects due to an increase in daytime somnolence.¹⁴ In the GA²LEN position paper,¹⁵ it is strongly recommended not to use first-generation antihistamines any longer in allergy both for adults and children. Two studies have investigated the effects of increased doses of desloratadine in patients with CU. In a prospective, randomized, placebo-controlled, crossover study of patients with acquired cold urticaria, Siebenhaar *et al.*¹⁶ found that desloratadine at four times the standard dose significantly reduced acquired cold urticarial lesion severity as compared with 5 mg of desloratadine. Furthermore, desloratadine at four times the standard dose did not increase the rate of somnolence. Staevska *et al.*¹⁷ studied 80 patients with CU in a randomized, double-blind design of levocetirizine and desloratadine. The conventional daily dose of 5 mg was initially administered, and doses were increased weekly to 10 or 20 mg if relief of symptoms was unsatisfactory. Patients who did not respond to 20 mg of one of the antihistamines were switched to 20 mg of the other one. Thirteen patients, nine in the levocetirizine group and four in the desloratadine group, became symptom-free at the 5-mg dose, and 21 responded to 10 mg, eight to levocetirizine, seven to desloratadine, and 20 mg, five to levocetirizine and one to desloratadine. Seven of 28 patients who did not respond to 20 mg of desloratadine responded to 20 mg of levocetirizine, whereas none of the 18 levocetirizine nonresponders improved with desloratadine at 20 mg. In addition, increased antihistamine doses improved patient quality of life without increasing somnolence. The authors concluded that increasing levocetirizine and desloratadine doses by up to fourfold improved chronic urticaria without affecting safety in

approximately three-quarters of patients with difficult-to-treat chronic urticaria. In a subgroup of desloratadine, the percentage of patients who were symptom free was 10% (5 mg/day), 17.5% (10 mg/day) and 2.5% (20 mg/day). From this study, 83.1% of the patients needed desloratadine above the standard dose to completely control the symptoms. It was found that CSU with antithyroid antibodies or high ESR more than 20 mm/h was associated with nonresponders treated by conventional doses of desloratadine. Twenty-seven (38.0%) at 10 mg, 15 (21.1%) at 15 mg, and 13 (18.3%) at 20 mg of these patients completely responded to desloratadine. Four (5.6%) patients did not get remission even taking a fourfold dose of the standard dose in this study, while 45% (18/40) of the remaining patients from the study of Staevska *et al.*¹⁷ had symptoms at 20 mg of desloratadine. The duration for up-dosing was 1 week in that study and 2–4 weeks in this study. According to the EAACI/GA²LEN/EDF/WAO, they suggest a 2-week evaluation before up dosing; a 1-week interval may, therefore, be too soon to adjust the dose. While up-dosing the antihistamines for the treatment of CU is generally accepted, there is little mention about the maintenance period of treatment or regimen guidelines for dose de-escalation once the disease is in remission. In the study herein, once CSU was completely controlled (UAS7 = 0), 94% of the patients developed recurrence of the disease if the treatment was stopped immediately. The symptoms, however, recurred in 65.1% of the patients even if the patients still received desloratadine at the same dose, inducing remission for a further 4 weeks. Interestingly, if the same dosage was maintained for a further 8 weeks before decreasing the dose, the recurrence rate dropped to 4.9%. It can therefore be suggested that once the disease is completely controlled, the same treatment should not be stopped or the dosage reduced immediately but should be maintained for at least 8 weeks before dose reduction in order to prevent the occurrence of the symptoms. CSU patients, however, may have spontaneous remission or intermittent exacerbation during the course of the disease. The study of Champion *et al.*¹⁸ found that in 554 patients, approximately 50% of patients without angioedema had spontaneous remission within 1 year, with 20% having had intermittent exacerbations over a 2-year duration, and 45% of patients with CU had persistent disease longer than 1 year. Kulthanan *et al.*¹⁹ reviewed 450 patients with CSU and reported that 34.5% had disease remission within 1 year, and the median disease duration was 390 days. Therefore, a longer follow-up period after disease is controlled with second generation H1-antihistamines is required.

In conclusion, nonsedating, selective, H1-receptor antagonists are still the mainstay for the treatment of CU. Most patients from this study, however, required modern second-generation antihistamine at a higher than standard dose for getting remission. Even though the patients received high doses, the adverse effects were mild and reversible. In addition, once the disease was completely resolved, an 8-week maintenance

period before dose de-escalation is suggested in order to decrease the recurrence rate. The limitation of this study is that the retrospective information from the medical records may be inadequate and duration of the follow-up may be not long enough. Further prospective research, therefore, with long-term follow-up is required to clarify this point.

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