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A Study of Patients with Chronic Idiopathic Urticaria from a Medical Center in Northern Taiwan

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Background: Chronic idiopathic urticaria (CIU) is a common dermatological disorder which significantly affects the quality of life of patients worldwide. This study investigates the demographic features, laboratory findings and the response to treatment of CIU patients prospectively in a medical center in northern Taiwan. **Methods and Results:** Thirty-three patients (15 females, 18 males, median age 32.79 years) with CIU were included according to the protocal approved for this study. A laboratory survey, including complete blood cells (CBC) with differential count, erythrocyte sedimentation rate (ESR), biochemistry panels, autoimmune profiles, thyroid function and multiple allergy simultaneous test (MAST) were conducted and analyzed before and after once daily monotherapy with levocetirizine 5mg. In addition, therapeutic efficacy was also assessed using mean pruritus score (MPS) and the mean number of wheals (MNW) score. The most commonly found reactive agents in the specific allergen test were mite DF (18/33 subjects, 54.4%) and mite DP (18/33 subjects, 54.4%). No significant difference was noted before and after levocetirizine monotherapy in terms of CBC, AST, ALT, BUN, creatinine, and ESR. Furthermore, the result of the MAST was also not affected by levocetirizine treatment. Compared to the therapeutic outcome measured on day-8, administration of antihistamine treatment significantly decreased MPS and MNW scores during day-22, day-29, and day-30. Consistently, the mean scores of MPS and MNW were significantly lower on day-36 than on day-8 within the same IgE level. **Conclusions:** Most of the patients in this study experienced satisfactory clinical improvement after once daily monotherapy with levocetirizine 5mg, whereas the antihistamine treatment did not result in a statistically significant change in the laboratory investigations. This study demonstrates that exhaustive investigations may not be necessary for patients with CIU and should be reserved for individuals following acquisition of a detailed history and physical examination. However, the monotherapy with low-sedative levocetirizine demonstrated a good clinical efficacy and did not significantly alter the laboratory parameters including the result of MAST. Therefore, it is suggested that MAST be included for checking which allergens should be avoided.

Key words: chronic idiopathic urticaria, laboratory investigation, levocetirizine, therapeutic efficacy

INTRODUCTION

Chronic idiopathic urticaria, a relatively common skin condition, defined by the continuous or recurrent attacks of wheals and/or angioedema which persisted longer than 6 weeks, with no known attributable etiology. The recurrent itchy skin lesions have a negative impact on the quality of life of CIU patients. Many affected patients search for an accurate etiology that has triggered the onset of their disease through numerous clinical visits. However, opinions among physicians concerning the appropriate laboratory investigations for these patients are the subject of debate. Most reported clinical studies of antihistamine have been focused on the therapeutic efficacy and side effects, but few have been concerned with whether antihistamine alters the laboratory parameters. In addition, H2 antihistamine is known to have immunomodulatory properties[1], but no study has tested whether

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Table 1 Inclusion/exclusion criteria of our study

Inclusion Criteria (participants were required to fulfill all items)
1). Aged 12-65 years with a diagnosis of chronic idiopathic urticaria (CIU) at least 3 months before study entry
2). Having a minimum of 1 to 5 wheals, confirmed by the physician, on the day of screening (assigned day 1)
3). Mild to moderate severe itching during the previous 12 hours
4). The informed consent must be signed by the patient. If the patients ages between 12~20 years, his/her legal representative must also sign this agreement form
Exclusion Criteria (none of the following items allowed)
1). Urticaria associated with an underlying systemic disease
2). Physical urticaria
3). Urticaria caused by medications, insect bites, food, or other known cause;
4). Drugs or alcohol abuse
5). Those with blood dyscrasia, malignancy, malabsorption, or chronic infection
6). Clinically significant psychiatric, cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease
7). Female patient plans to be pregnant or lactating
8). Subjects have a past history of asthma or allergic rhinitis

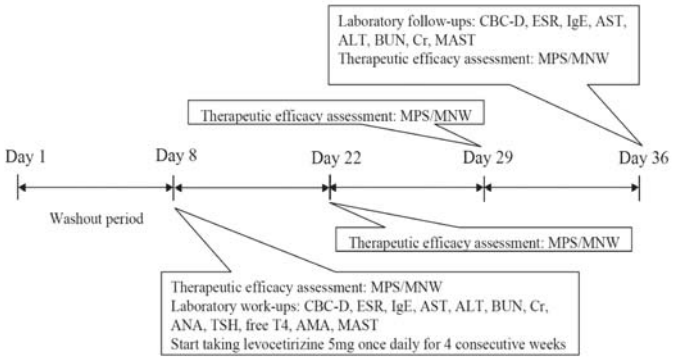

Fig. 1 Summary of study design and timing of investigative assessments

H2 antihistamine alters the data for a specific allergen test and IgE level. Moreover, few data apply to the clinical features of patients with CIU in Taiwan. Herein, a prospective investigation of the demographic features, laboratory findings and response to treatment of CIU patients in a single medical center in northern Taiwan is conducted. In addition, the relationship between antihistamine treatment and changes in laboratory parameters was also determined.

METHODS

This prospective study was conducted at the Department of Dermatology, Tri-Service General Hospital in Taiwan from October 2010 to October 2011 and was approved by the Institutional Review Board/Ethics Committee of the Tri-Service General Hospital (TSGHIRB approval number: 099-05-034). Informed consent was obtained from those who underwent investigations. Thirty-three patients who met pre-dosing evaluation and enrollment criteria (Table 1) were recruited for this study. Shown in figure 1 is the summary of design of the study and the timing of the investigative assessments, including outcome measures and laboratory data collections. On their assigned Day-1 (screening day) each participant was asked to discontinue current medication, especially antihistamines and corticosteroids, for at least a 7-day washout period, before exposure to the levocetirizine monotherapy used in this study. On Day-8 (before treatment), all participants underwent a series of laboratory work-ups consisting of complete blood cells with differential count (CBC-D), erythrocyte sedimentation rate (ESR), immunoglobulin E (IgE), aspartate aminotransferase (AST), alanine transferase (ALT), blood urea nitrogen (BUN), creatinine (Cr), antinuclear antibody (ANA), thyroid stimulating hormone (TSH), free T4, anti-thyroid microsomal antibody (AMA) and a multiple allergy simultaneous test (MAST) to 36 common food allergen, dust, mites, pollen and fungi. In addition, general physical examinations and medical and drug histories were obtained, at the same time. The patients were then treated with the low-sedative second-generation antihistamine, levocetirizine 5 mg, monotherapy once daily for 4 consecutive weeks. The primary therapeutic efficacy variable was defined as the change from baseline in mean pruritus score (MPS), over four weeks, as recorded by each participant every day. Pruritus severity was self-assessed and rated on a scale from 0-4, where 0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying and troublesome, may interfere with sleep/daily activities; 3 = severe, very annoying, substantially interfering with sleep/daily activities and 4 = very severe, warrants a physician visit. Another therapeutic efficacy variable was defined as the change from the baseline in the mean number of wheals score (MNW), every day for four weeks. The number of wheals was rated on a scale of 0-4, where 0 = none; 1 = 1-5 wheals; 2 = 6-15 wheals; 3 = 16-25 wheals and 4 = >25 wheals. Each patient had follow-up visits on the Day-22 (Total treatment duration: 14 days), Day-29 (Total treatment duration: 21 days) and Day-36 (Total treatment duration: 28 days), for the evaluation of therapeutic efficacy. These two efficacy measures

Table 2 Summary of the results of multiple allergy simultaneous test (MAST) (n=33)

Allergen	Number (%)
Mite DF	18 (54%)
Mite DP	18 (54%)
Housedust	10 (30%)
Cat	6 (18%)
Cockroach Mix	5 (15%)
Dog	5 (15%)
Shrimp	4 (12%)
Crab	4 (12%)
Ragweed Mix	3 (9%)
Penicullium	3 (9%)
Alternaria	3 (9%)
Aspergillus	2 (6%)
White Mulberry	2 (6%)
Pigweed	2 (6%)
Eucalyptus	2 (6%)
Chicken feathers	2 (6%)
Bermuda Grass	2 (6%)
Soybean	2 (6%)
Milk	2 (6%)
Cladosporium	1 (3%)
Yeast	1 (3%)
Egg yolk	1 (3%)
Egg white	1 (3%)
Codfish	1 (3%)
Peanut	1 (3%)
Beef	1 (3%)
Wheat	0
Latex	0
Tuna	0
Clam	0
Cheese	0
Avocado	0
Pork	0
Willow, Black	0
Japanese Cedar	0
Timothy Grass	0

have been used in previous studies.[2] Laboratory follow-ups including CBC-D, ESR, IgE, AST, ALT, BUN, Cr and MAST were conducted at the last visit (visit 5) and the relationship between drug intervention and changes in the laboratory parameters were analyzed accordingly.

Table 3 The basic characteristic comparisons for before and after levocetirizine treatment (n=33)

Variables	Day-8 (Before treatment)	Day-36 (After treatment)	P value
CBC			
WBC	6.09± 1.59	6.07± 1.38	0.92
RBC	4.60± 0.36	4.65± 0.42	0.13
Platelet	244.39±40.98	248.03±50.98	0.35
Neutrophil	58.48±6.98	60.21± 8.64	0.25
Lymphocyte	30.56±6.80	29.60± 7.59	0.45
Monocyte	7.55±1.94	6.94± 1.93	0.06
Eosinophil	2.87±2.04	2.83± 2.35	0.86
Basophil	0.53±0.42	0.42± 0.21	0.15
AST (U/L)	19.88± 5.53	20.91±6.41	0.34
ALT (U/L)	20.30±13.26	22.58±18.03	0.45
BUN (mg/dl)	12.73± 3.14	12.64±3.07	0.86
Creatinine (mg/dl)	0.78± 0.16	0.80±0.15	0.16
ESR	5.97±4.88	6.00± 0.21	0.95
IgE (IU/ml)			
IgE ≦165	23(69.7%)	24(72.7%)	0.78*
IgE ＞165	10(30.3%)	9(27.3%)	

*Chi-squared tests for categorical variables.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). For paired comparisons, CBC, AST, ALT, BUN, creatinine, ESR, IgE and MAST were statistically examined using paired t-tests, for continuous variables and chi-squared tests for categorical variables. Generalized Estimating Equations (GEEs) have become common in the analysis of correlated data, in which subjects are measured at different times. In this study, GEE was used to compare two groups (IgE >165 and IgE ≤ 165) and explore the effect of time on the MPS or MNW within the same IgE level. In addition, GEE determine whether there is a pairwise comparison in the treatment effect using the post-hoc procedures of the least significance difference (LSD) test. In all analyses, a value of $p < 0.05$ was considered to be statistically significant. Finally, the curves for the changes in MPS and MNW scores were plotted for all time points.

RESULTS

Thirty-three patients (male: 18, female: 15; mean age: 32.79, range: 21-59 years) were recruited for this study.

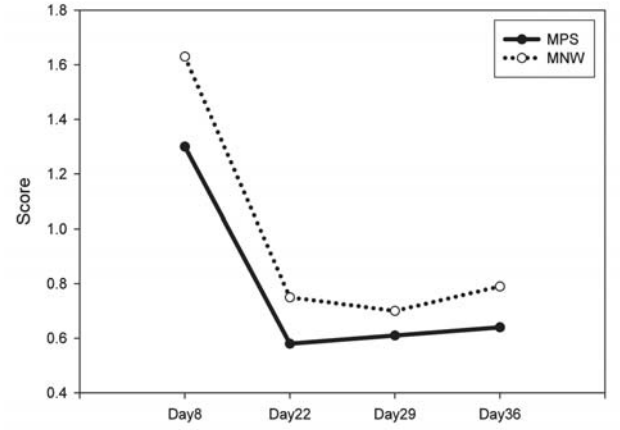

Fig. 2 The variations of MPS and MNW score during treatment periods.

Table 4 Results of GEE analysis examining the changes of MPS and MNW in the different time

Variables	Day-8	Day-22	Day-29	Day-36	P-value
MPS	1.30±0.25	0.58±0.11*	0.61±0.14*	0.64±0.14*	< 0.050.
IgE≦165	1.13±0.27	NA	NA	0.61±0.17*	< 0.05
IgE>165	1.70±0.50	NA	NA	0.70±0.21*	< 0.05
MNW	1.61±0.27	0.73±0.14*	0.70±0.15*	0.79±0.17*	< 0.001
IgE≦165	1.50±0.30	NA	NA	0.77±0.20*	< 0.001
IgE>165	1.86±0.50	NA	NA	0.84±0.29*	< 0.05

GEE = Generalized Estimating Equation; IgE (IU/ml); MPS=mean pruritus score; MNW=mean number of wheals; NA= non application

P value indicated the effect of time on the MPS or MNW within the same IgE level.

*Reference group: Day-8

The mean systolic and diastolic blood pressure was 121.6 and 72.6 mmHg, respectively. The body mass index (BMI) of these subjects fell within 18-24, for 75.6 % of all enrolled patients. Two patients (6%) had abnormal CBC-D (one with neutrophilia, another with eosinophilia). Four patients (4/33 subjects; 12%) had abnormal liver function indicated by elevated level of AST/ALT. One patient (3%) had abnormal thyroid function indicated by TSH/free T4. Two patients (2/33 subjects; 6%) had an elevated level of ESR. The IgE level was elevated (the normal IgE level was defined as a level of no more than 165 IU/ml) in 10 patients (10/33 subjects; 30%). One patient (3%) had abnormal ANA with a speckled pattern (abnormal ANA was defined by a titer >1:100). None had abnormal AMA. Twenty-nine patients (29/33 subjects; 87.9%) exhibited hypersensitivity to at least one specific allergen. The percentage of individual allergen hypersensitivity is summarized in Table 2. The most common allergen seen in this cohort was mite *Dermatophagoides farinae* (DF; 18/33 subjects, 54.4%) and mite *Dermatophagoides pteronyssinus* (DP; 18/33 subjects, 54.4%). As shown in Table 3, antihistamine treatment did not result in a statistically significant change in the mean CBC-D and major biochemical parameters. Interestingly, the incidence of abnormalities in specific allergen test was also not found to be altered by the treatment. Compared to the initial therapeutic outcome measure, administration of antihistamine treatment (levocetirizine 5 mg once daily for 4 weeks) significantly decreased the MPS and MNW scores, during day-22, day-29 and day-36 (Figure 2). Further analysis of the MPS and MNW scores of the patients showed that their mean value of MPS and MNW was significantly lower on day-30 than on day-8 (Table 4).

DISCUSSION

Chronic urticaria is a common dermatological disease, which is characterized by recurrent or persistent, itchy, variably-sized, raised wheals with or without angioedema, spanning over 6 weeks of duration. It has a significant impact on quality of life, to an extent that is comparable to patients suffering from ischemic heart disease.[3] Its prevalence has been reported to range from 0.05% to 3% in previous surveys.[4] The majority of chronic urticaria patients have no identifiable etiology. These cases are referred to as "chronic idiopathic urticaria" (CIU). Thirty-three patients were enrolled in this study. A slight preponderance towards males (M:F = 1.2:1) was noted in this study, which is different from most western and Asian studies that show a female predominance.[5-6] The reason for this may be the small sample size of the cohort. The average age of the patients was 33.3 years (ranging from 21-59 years), which is similar to the age distribution of previous studies.[4,6]

Controversy surrounds the appropriate choice of laboratory investigations for CIU patients because past studies showed very few abnormalities in laboratory findings in these patients.[7] This cohort also shows a low percentage of abnormalities in CBC (6%) as well as other biochemical parameters (ranging from 6% to 12%). This result is in agreement with a recent large retrospective analysis of chronic urticaria patients, which concluded that laboratory testing in these patients rarely lead to

changes in management that result in improved outcomes. Therefore, routine extensive laboratory work-ups for CIU patients should be discouraged and reserved for individuals following the acquisition of a detailed history and physical examination. Of the immunologic laboratory investigations performed, the most prevalent finding was an elevated IgE level present in up to 30% of the participants. This prevalence is similar to that observed by earlier studies, conducted in other countries.[8-9] It has recently been shown that elevated serum total IgE may be a potential marker for severe chronic urticaria, whereby the elevated level of total serum IgE is correlated with the severity and duration of clinical manifestations.[8] In this study, it was also found that patients whose IgE level was elevated before taking levocetirizine exhibited a significantly lower mean value of MPS and MNW on day-30 within the same IgE group (Table 4). These findings suggest that IgE may not be used as a marker to monitor the severity of the disease in chronic urticaria patients. However, further large, well designed controlled clinical trials must be conducted before any conclusion can be drawn.

The majority of the patients for this study (87.9%) had hypersensitivity to at least one specific allergen as indicated by a specific allergen test. The most common allergens seen in our participants were mite DF (54.4%) and mite DP (54.4%). However, antihistamine treatment did not alter the result of allergen hypersensitivity test for these patients. These results were used to confirm the real allergen to the patient via a more specific allergen challenge test. This could further benefit patients if they could more strictly avoid allergens even during the antihistamine treatment. Little attention has been paid to the possibility that antihistamine treatment could alter the laboratory parameters in CIU patients. This study shows that antihistamine treatment did not result in a statistically significant change in the mean CBC-D and major biochemical parameters (Table 3). It suggests, at least in this cohort, that routine extensive laboratory follow-ups after antihistamine treatment seem to be unnecessary.

Low-sedative, second-generation antihistamine has been the drug of choice in the management of chronic urticaria. Many clinical experts and several professional societies have issued evidence-based recommendations supporting the use of this class of drugs.[10-12] Levocetirizine, a R-enantiomer of cetirizine dihydrochloride, is a potent antihistamine that has a fast onset and long duration of antihistaminic effect due to its rapid absorption and high bioavailability. It is licensed in Taiwan as 5 mg tablets for use in adults and children over 6 years of age for the symptomatic relief of urticaria and allergic rhinitis. In addition to its antihistaminic property, levocetirizine has also been found to have an anti-inflammatory effect with both *in vivo* and in vitro evidence.[13] It is worthy of note that an interesting study demonstrated the association between clinical improvement in chronic urticaria patients, following levocetirizine treatment, and a reduction in the levels of the circulating adhesion molecules, P-selectin and E-selectin.[14] A positive correlation was observed and it was hypothesized that a reduction in the expression of adhesion molecules expression by endothelial cells might result in anti-inflammatory effects through inhibition of leukocyte adhesion and extravasation in chronic urticaria patients.[14] ESR is a marker of inflammation, and the level of ESR was also measured before and after the administration of levocetirizine in this study. The mean level of ESR did not show a statistically significant difference, before and after levocetirizine treatment. However, it was observed that the levocetirizine did result in the normalization of the ESR level in the only 2 patients who initially showed an elevated ESR level (2/2 subjects; 100%). The decrease in ESR is also associated with the clinical improvement in these two patients. This observation suggests that a subset of CIU patients might benefit from the treatment because of the intrinsic anti-inflammatory property of levocetirizine.

In conclusion, this study demonstrates a clinical and laboratory evaluation of CIU patients in a medical center in northern Taiwan. There was slight predominance of males in the cohort. Few patients had abnormal CBC-D or major biochemical tests. Levocetirizine monotherapy neither significantly altered the incidence of a specific allergen test, nor did it change the most of the laboratory parameters. Routine exhaustive pre-treatment laboratory work-ups and post-treatment follow-ups should be restricted and limited to those with an abnormal history or physical examination. This study was limited by the small sample size and short duration. Further large, controlled, well-designed, multicenter studies are warranted to confirm these findings.

DISCLOSURE

This IRB-approved study was funded by Yi-Chuan Pharmaceutical Co., Taiwan. There were no conflicts of interests for all authors.

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