

ORIGINAL ARTICLE

Efficacy of leukotriene receptor antagonist with anti-H1 receptor antagonist plus anti-H2 receptor antagonist for treatment of refractory chronic idiopathic urticaria

Kong-Sang Wan^{1,2} and Yung-Sen Chang¹¹Department of Pediatrics, Taipei City Hospital, Renai Branch, Taiwan and ²College of Medicine, National Yang Ming University, Taipei City, Taiwan

Abstract

Background: The efficacy of the combination of leukotriene receptor antagonist (LRA) and H1 antihistamine was similar to the synergistic regimen of H1 and H2 antihistamine for treatment of chronic idiopathic urticaria (CIU). However, the effective rates of these two regimens were only 53.3% and 63.3%, respectively.

Method: A total of 50 with two combined therapeutic regimens treatment ineffective patients were evaluated. Patients were single blinded and randomly assigned to one of two medication groups that received the following regimens for 4 weeks: Group A ($n = 30$), combination of LRA, H1 antihistamine and H2 antihistamine. Group B ($n = 20$) continued with the previously taken two combination regimens. The treatment efficacy was measured by daily urticaria activity score (UAS) of wheal and itch. A positive therapeutic response was defined as a reduction to <25% of baseline weekly UAS, while a relapse was a return to >75% of baseline weekly UAS.

Results: At the end of 4 weeks, the UAS response to treatment of Group A was decreased from 35.2% to 21.2%, and the Group B was persisted with 33.9% as before the treatment.

Conclusion: The combination of LRA, H2 antihistamine and H1 antihistamine is promising for the refractory CIU cases, which were refractory for two combined therapeutic regimens.

Keywords

Antihistamine, chronic idiopathic urticaria, montelukast, treatment

History

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Introduction

Chronic idiopathic urticaria (CIU) is a widespread wheals daily or almost daily for at least six weeks and absence of a causative physical or environmental trigger (80% to 90% of patients). About 40–50% of patients were associated with angioedema (AE) and 10% of the patients experienced only AE without hives (1,2). The prevalence of this disorder is about 0.1–3% of all people in the United States and Europe, and it is believed to be the same throughout the rest of the world (3,4).

The etiology of CIU is unknown. In 30–50% of patients, CIU is associated with autoantibodies against the α -chain of the high-affinity IgE receptor FC ϵ RI present mast cells or IgE molecule that lead to mast cell and basophil activation, thereby giving rise to the release of histamine and other proinflammatory mediators. Thus, emerging evidence suggests that the CIU is a mast cell autoimmune disease (5,6). The Altman study showed that another mechanism contributing to the possible pathogenesis of CIU is dysregulating of intracellular signaling pathways involving Sky, AHIP-1 or SHIP-2 in basophils and mast cells (7).

The diagnosis of CIU requires a detailed patient history and comprehensive examination, with additional testing tailored to the patient's history. H1 antihistamines, H2 antihistamines, antileukotrienes and corticosteroids constitute the main pharmacologic

treatment modalities. However, traditional options may be exhausted by the refractory CIU patient and immunosuppressive drugs may be used, most commonly cyclosporine. More recent experimental studies have also suggested that omalizumab, an anti-IgE therapy, may be beneficial (8–14).

CIU is rarely permanent, and that almost 50% of patients undergo remission within one year (15). However, there are no spontaneous remission in the study Group A and placebo control Group B in the beginning of the study. Up to 40% of patients who have CIU for more than 6 months still have urticarial wheal 10 years later (16). Studies in dermatology clinics in multiple countries report complete resolution in approximately one-third of patients with CIU over 1 to 5 years and partial improvement in another third (15). Moreover, CIU can cause persistent debilitating symptoms and affects patient's quality of life. In Maiti study, it showed 27.3% decrease in Aeries quality of life questionnaire score (17). Therefore, it is important to find out a safety and effective therapeutic strategy for CIU, especially for the refractory type. We hypothesized that a combination of H1 anti-histamine, H2 anti-histamine and LRA may be a promising therapeutic regimen.

Material and methods

A total of 50 refractory CIU patients who were treated with two combined therapeutic regimens were single blinded and randomly assigned to two groups after obtaining informed consent. The randomization of the participants of two medication groups was done using computer-generated random numbers and the

Correspondence: Dr Kong-Sang Wan, Department of Pediatrics, Taipei City Hospital-Renai Branch #10, Section 4, Renai Road, Da An District, Taipei City 106, Taiwan. Tel: +886 2 2709 3600, ext.3471. Fax: +886 2 2704 6356. E-mail: gwan1998@gmail.com

participants within each stratum were randomized by using opaque-sealed envelopes to one of the two medication groups. Each group had a one-week “run-in” period to wash out the previous treatment medication. In Group A ($n = 30$), each patient received a combination of H1 anti-histamine, H2 anti-histamine and LRA for 4 weeks. In Group B ($n = 20$), original two combined regimens were given to the participants for 4 more weeks.

The urticaria activity score (UAS) is a widely used patient-reported outcome measure for patients with CIU that includes two items: intensity of pruritus and number of hives. Moreover, enhanced UAS7 is calculated as the sum of pruritus and number of hives over 1 week, which showed adequate measurement properties to support its use in clinical research (18). Patients completed a daily record for the preceding 24 h of the number of small (diameter <3 cm) and large (>3 cm) skin wheals, according to a specific classification number, and with scoring as follows: 0, no wheals; 1, <10 wheals; 2, 10–15 small wheals or <10 large wheals; 3, almost entirely covered with wheals. The relative severity of itch was scored as: 0, none; 1, mild; 2, moderate; 3, severe. The possible weekly aggregate UAS therefore ranged from 0 to 42.

Patients also provided a 10-cm visual analog scale score (VAS) form 0 (none) to 10 (worst) during each outpatient clinic visit that indicated the overall severity of their urticaria over the previous 2 weeks. A response to medication was defined as a reduction of weekly UAS to $<25\%$ of baseline and a relapse as a return to $>75\%$ of baseline UAS. Response of VAS score was calculated and compared to show the difference before and after treatment of the study groups.

The Statistical Package for the Social Sciences (version 1.0 for Windows; SPSS Inc., Chicago, IL) programs processed the resulting data. A p value of <0.05 was considered to be significant.

Results

Fifty refractory CIU patients were randomized for treatment, with 30 patients allocated to Group A and 20 patients to Group B (Table 1). Patients' compliance was excellent, no participants dropped out after experiencing, no real benefit following therapy. Comparing the treatment results of two treatment groups, there was significantly improved UAS in the combination of LRA, H1

antihistamine and H2 antihistamine Group A and no any improvement of UAS in the two combined regimen Group B ($p < 0.05$). The improvement percentage as measured by the UAS for Group A was 66.7% (Table 2).

Discussion

The most popular theory to explain the development of chronic urticaria is referred to as the autoimmune hypothesis. The suggestion that CIU may have an autoimmune basis came from the recognition that thyroid autoantibodies and thyroid dysfunction were observed more commonly in patients with CIU (19). Moreover, autoimmune thyroiditis (AT) is more prevalent in patients with CIU than in the general population. Previous small studies without any controlled comparison reported that CIU remits in patients with CIU and AT treated with l-thyroxine but in Magen's Study, 3 and 6 months of l-thyroxine treatment had no effect on the course of CIU in patients with CIU and AT (20).

Montelukast might be effective in chronic urticaria when taken with an antihistamine. On a molar basis, leukotrienes are 100 times more potent than histamine, and intradermal leukotrienes D4 (LTD4) injection causes a wheal-and-flare response that could be inhibited by LTD4 antagonist (21). Montelukast is a new selective receptor antagonist of LTD4, and its administration orally once a day was recently shown to be very effective in the treatment of cold urticaria (22) and delayed pressure urticaria (23). Nettis et al. have also demonstrated that montelukast had better therapeutic effects compared with those of fexofenadine for CIU, and the majority of the patients with positive ASST results were unreactive after montelukast therapy of 30 days (24).

H1 antihistamines are the cornerstone of pharmacotherapy for chronic urticaria and second-generation antihistamines are recommended as first-line therapy because of their high degree of efficacy and safety (1,25). Differences in duration of *in vivo* receptor occupancy may affect the potency of H1 antihistamine. Levocetirizine appears to have greater *in vivo* H1 receptor occupancy compared with later generation H1 antihistamines, which may confer an advantageous efficacy/safety profile. This has been confirmed in a recent head-to-head study showing that levocetirizine was more effective than desloratadine in improving pruritus in CIU patients. Fexofenadine has been shown to have a low occupancy of H1 antihistamine receptors in the brain, which reduces the likelihood of sedation (26). Moreover, H1 and H2

Table 1. Characteristics of the study participants.

	Group A Cetirizine + Famotidine + Montelukast	Group B Cetirizine + Cetirizine + Famotidine Montelukast	p Value
Number of patients	30	10 10	NS
Means age (years)	34.8 (20–54)	36.4 (20–52) 34.8 (20–54)	NS
Sex (M/F)	13/17	4/6 3/7	NS
Time since onset of urticaria (months)	21.2 (10–35)	20.3 (7–30) 22.5 (12–28)	NS
Mean baseline UAS	35.2 (30–42)	33.9 (30–38) 34.9 (30–40)	NS

UAS = urticaria activity score; NS = nonsignificant.

Table 2. Reduction in urticaria activity score (UAS) of the two study groups after 4 weeks of treatment.

	Baseline UAS (n)	UAS after 4 weeks of treatment (n)	Positive therapeutic response reduction to $<25\%$ of baseline UAS (%)	p Value
H1RA + H2RA + LRA (Group A)	35.2 (30)	21.2 (20)	66.7%	<0.05
H1RA + H2RA/H1RA + LRA (Group B)	33.9 (20)	33.9 (20)	0%	NS

UAS = urticaria activity score; H1RA = H1-receptor antagonists; H2RA = H2-receptor antagonists; LRA = leukotriene receptor antagonist; NS = nonsignificant.

antihistamine combinations have used agents that are metabolized by the same liver enzymes, raising the possibility that the benefit was largely due to increased serum concentrations of one or both drugs, rather than a true synergistic effect (27). Thus, a trial of H2 antihistamines can be considered as additive therapy in patients whose symptoms do not respond adequately to H1 antihistamines alone.

However, the traditional treatment options (antihistamines, leukotriene inhibitors and immunosuppressives) may be exhausted by refractory CIU, and the effective rates of the above two combination treatment strategies, antihistamine plus LRA, H1 antihistamine plus H2 antihistamine, were only 53.3% and 63.3%, respectively (11). In Kosnik study, they showed that in patients with antihistamine-resistant CU the addition of montelukast significantly diminished symptoms in only a small minority of patients (28). Also, chronic urticaria and angioedema may not respond to prednisone, and some of these patients may try methylprednisone (29). Therefore, for patients with severe unremitting CIU who have failed to benefit from conventional therapy with antihistamines, other effective and safe therapeutic modalities are required. There are no sedative side effects, no cardiotoxic effects and no hepatic metabolism in second-generation antihistamine, including the new H1 antagonist, bilastine. They are highly selective for the H1 receptor and with no apparent affinity for other receptors. The safety profile in terms of adverse effects is very similar to placebo in all phase I, II and III clinical trials (30). In this study, three combined regimen including H1 antihistamine, H2 antihistamine and leukotriene receptor antagonist (cetirizine 5 mg plus famotidine 20 mg plus montelukast 5 mg twice a day) were given to the refractory CIU patients who were treated with two combined therapeutic regimens for 4 weeks (Group A). A control group, 20 refractory CIU patients were given the origin two combined regimen for another 4 weeks (Group B). At the end of 4 weeks, the UAS response to treatment was 66.7% for Group A, and no real change for the placebo treatment Group B. Moreover, in Group A, 20 patients' mean VAS decreased from 6.57 $\pm$ 0.43 to 3.35 $\pm$ 0.64 after treatment. In opposite, in all the 20 patients in Group B, their mean VAS was maintained at 6.75 $\pm$ 0.25.

In conclusion, the combination of LRA, H2 antihistamine and H1 antihistamine is promising for refractory CIU cases, which were refractory for two combined therapeutic regimens.

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