

ORIGINAL ARTICLE

Retrospective cohort study on combination therapy with the histamine H2-receptor antagonist lafutidine for antihistamine-resistant chronic urticaria

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We conducted a retrospective cohort study evaluating the efficacy and usefulness of the addition of lafutidine, a novel histamine H2-receptor antagonist, in treatment of patients with idiopathic chronic urticaria whose disease was not well controlled with histamine H1-receptor antagonists. Based on the assessment of global improvement, moderate or better improvement was achieved in 39 of 46 patients (85%) after 1–3 weeks of additional administration of lafutidine and 35 patients (76%) after 3 months. No incidence of drug-related adverse reactions was reported in any patient. Lafutidine was rated as useful or better in 34 patients (74%) after 3 months of treatment. The usefulness of the drug was not affected by differences in background factors, such as disease duration, previous treatment duration and the number of concomitant H1-receptor antagonists. Lafutidine appears to be a promising addition to histamine H1-receptor antagonist therapy for the treatment of chronic urticaria resistant to treatment with H1-receptor antagonists alone.

Key words: chronic urticaria, H1-receptor antagonists, histamine H2-receptor antagonist, lafutidine, urticaria

Introduction

Urticaria is a disease characterized by the pathological appearance of transient and localized skin edema associated with erythema, known as wheals, which are often accompanied by severe pruritus. Chronic urticaria is defined as urticaria persisting for 1 month or more after onset. Cases with unidentified causes account for at least 80% of cases of chronic urticaria, and many cases are refractory to treatment, making chronic urticaria one of the difficult-to-treat dermatological disorders.

The basis of treatment for chronic urticaria is administration of histamine H1-receptor antagonists. However, effects of antihistamine treatment vary widely among individual patients, and the response may be inadequate. In those cases, treatment is supplemented with adjuvants, such as histamine H2-receptor antagonists, leukotriene receptor antagonists, antianxiety drugs and Chinese herbal drugs (1).

We herein report a retrospective cohort study on the efficacy of lafutidine (Protecadin[®]) (2) a second-generation H2-receptor

antagonist launched in 2000, as a adjuvant therapy in patients with chronic urticaria who responded inadequately to H1-receptor antagonists alone.

Subjects and methods

Subjects

We conducted a retrospective study of patients responding inadequately to H1-receptor antagonists for treatment of chronic urticaria who visited the Department of Dermatology/Allergy at Juntendo Nerima Hospital in Tokyo, Japan from October 2009 to December 2010 and who were administered twice-daily 10 mg lafutidine (Protecadin[®]; Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) as adjuvant therapy. Inclusion criteria were the following: (i) urticaria of unidentified cause of at least 1 month duration, (ii) resistance to treatment with H1-receptor antagonists alone administered for 1 week or more at previous hospitals or ours; (iii) continued treatment with H1-receptor antagonists at unchanged doses while receiving lafutidine therapy and (iv) age 18 years or older. Exclusion criteria were (i) identified cause of urticaria, such as cholinergic, thermal, cold, factitious and solar urticaria; (ii) oral administration or injection of steroid within 2 weeks before initiation of lafutidine therapy; (iii) desensitization therapy disease; (iv) serious concomitant disease and (v) previous treatment with other adjuvants listed in the practice guidelines for urticaria (1).

Methods

We searched medical records of the Department of Dermatology/Allergy at Juntendo Nerima Hospital to identify patients who met the inclusion/exclusion criteria described above. Data culled from the records included sex, age, disease duration, past and family history of allergic diseases, complications, treatment for chronic urticaria before the start of lafutidine administration, usage of drugs that might affect drug evaluation.

The endpoints were two items of pruritus and erythema/wheel that were examined 1–3 weeks and 3 months after the start of lafutidine administration. The physicians in charge of the patients assessed changes in conditions following administration of lafutidine based on global improvement. Moreover, adverse reactions were investigated.

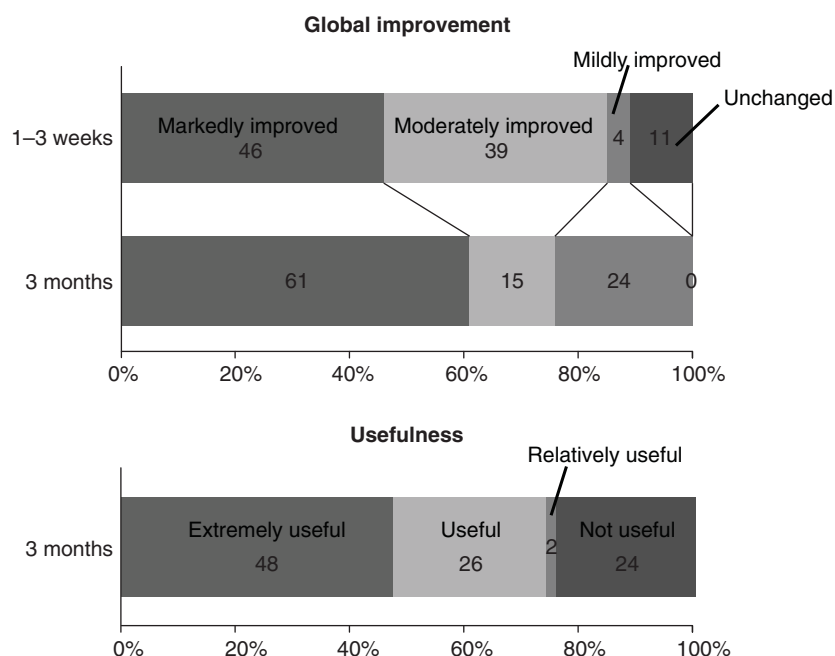


Figure 1. Treatment outcomes. After 3 months of treatment, lafutidine was assessed as useful or better (i.e., grade 4 or 5) in 74% of the patients. No adverse reactions were reported, and the drug was not assessed as harmful in any patients.

Pruritus was assessed in 4 grades: 0, no symptom; 1, itchy; 2, unable to resist scratching and 3, unable to sleep due to itching. Wheal was assessed in 4 grades: 0, not itchy; 1, a little itchy; 2, poor appearance and 3, severe. Based on the above two items, global improvement was assessed in 5 grades: markedly improved, moderately improved, mildly improved, unchanged and deteriorated. In consideration of global improvement and safety, the usefulness of the treatment was assessed in 5 grades (extremely useful, useful, relatively useful, not useful and harmful) after 3 months of treatment.

Results

From examination of the medical charts, we identified 46 patients (17 men and 29 women) who met the study's inclusion/exclusion criteria. Ages of the patients in the study population ranged from 18 to 76 years (mean: 47.7 years). Twenty-one patients reported disease duration of 1–6 months, and 25 patients reported disease duration of 6 months or more. Twenty-seven patients had no personal history or family history of allergic diseases. The previous treatment duration was less than 1 month in 26 patients, and 1 month or more in 20 patients. Regarding previous exposure to oral H1-receptor antagonists, 34 patients had received treatment with only one drug from that class, 10 patients had received treatment with two drugs from that class, and 2 patients had received treatment with three drugs from that class.

Based on the grades of pruritus and erythema/wheal, global improvement was rated as markedly improved in 21 patients (46%), moderately improved in 18 patients (39%), mildly improved in 2 patients (4%) and unchanged in 5 patients (11%) after 1–3 weeks of treatment. Global improvement after 3 months of treatment was rated as markedly improved in 28 patients (61%) and moderately improved in 7 patients (15%). Drugs had been added/changed in 11 patients (24%) (Figure 1).

No adverse reaction to lafutidine was reported throughout the study period. Usefulness after 3 months of treatment was rated by

the doctor as extremely useful in 22 patients (48%) and useful in 12 patients (26%). Lafutidine was evaluated as relatively useful in only one case (2%) where urticaria relapsed after missing oral administration, and as not useful in 11 patients (24%) due to addition/changes of drugs. There was no case in which lafutidine was assessed as harmful. Useful or better results were achieved in 74% of the patients (Figure 1). Of the 22 patients showing an extremely useful result, the number of previously administered H1-receptor antagonists was one drug in 17 patients, two drugs in 3 patients, and three drugs in 2 patients. The disease duration was 1 year or more in 18 patients. In these patients, lafutidine was assessed as extremely useful in eight patients and useful in five patients.

The χ^2 test was used to separately analyze the usefulness of lafutidine by age, sex, disease duration, personal/family history of allergic diseases, previous treatment duration and the number of H1-receptor antagonists administered in the previous treatment. No significant differences were observed in any background factors.

Discussion

The basis of treatment for chronic urticaria is pharmacotherapy based on antihistamines, as well as identification and avoidance of causes and triggers. H1-receptor antagonists are the mainstay of pharmacotherapy for idiopathic urticaria, and many drugs of this class have been developed. When treatment responses to these drugs are inadequate, their doses are increased or other drugs are added. However, when these measures fail to yield adequate effects, treatment guidelines recommend the addition of adjuvants, such as H2-receptor antagonists, Chinese herbal drugs, antianxiety drugs, leukotriene receptor antagonists, diamino-diphenyl sulfone and tranexamic acid (1).

Lafutidine is the latest H2-receptor antagonist developed in Japan, typically used for treatment of gastric disease (2). The mechanism of action of H2-receptor antagonists is not clearly understood, but several hypotheses have been proposed (3): H2-receptor antagonists suppress erythema/wheal reaction by

binding with H₂-receptors on the blood vessels of the skin; H₂-receptor antagonists act in the liver to delay metabolism of concomitant H₁-receptor antagonists; H₂-receptor antagonists affect cell-mediated immunity by enhancing suppressor function; and H₂-receptor antagonists suppress gastric acid secretion, resulting in relief of rash.

Concomitant therapy with H₂-receptor antagonists is commonly used in daily practice as treatment for chronic urticaria (4–8). Outside Japan, randomized controlled studies have shown a combination of terfenadine and ranitidine (5) and a combination of chlorpheniramine and cimetidine (6) to be useful, based on randomized controlled studies. A report of another randomized controlled study suggests that a combination of hydroxyzine and cimetidine is not effective in treating chronic urticaria (9). There is a similar report in Japan (3); however, the small number of cases limits the usefulness of the findings. In fact, these drugs have not been approved for coverage by the Japanese National Health Insurance.

In the study population reported here, 85% of patients showed moderate improvement or better (i.e., grade 4 or 5) after 1–3 weeks of combination therapy with lafutidine, and 76% showed moderate improvement or better after 3 months. No adverse reaction was documented. After 3 months, lafutidine was assessed as useful or better in 74% of the patients. Our results also indicated that lafutidine is not affected by differences in background factors, such as disease duration, previous treatment duration and the number of concomitant H₁-receptor antagonists. Effects of lafutidine are reported to persist for a longer period compared to other H₂-receptor antagonists, and no significant drug interactions associated with the inhibitory activity against cytochrome P450, have been reported (10).

Outside Japan, combination therapy with H₂-receptor antagonists is not strongly recommended in the practice guidelines for urticaria because there are only a few relevant articles with high evidence levels (11). Large-scale randomized double-blind studies and long-term follow-up studies of combination therapy with H₁- and H₂-receptor antagonists may be necessary

for developing evidence-based treatment strategies in harmony with daily practices.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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