Comparison of antileukotrienes and antihistamines in the treatment of allergic rhinitis

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ABSTRACT

Background: The aim of this study was to compare the effect of antileukotriene (anti-LT), antihistamine, and a combination of anti-LT and antihistamine on the symptoms and nasal resistance in allergic rhinitis patients.

Methods: We performed a placebo-controlled study, with 120 persistent, moderate to severe allergic rhinitis patients randomly selected to receive the different treatments for 4 weeks: no treatment, 10 mg of cetirizine once per day, 20 mg of zafirlukast once per day, 20 mg of zafirlukast twice per day, a combination of 20 mg of zafirlukast and 10 mg of cetirizine once per day, or a combination of 20 mg of zafirlukast twice per day and 10 mg cetirizine once per day. The nasal secretion nitric oxide (NO) concentration, nasal symptom score, and nasal resistance were measured before and after treatment.

Results: Total symptom scores improved in each treated group compared with the control group (p < 0.05). Nasal obstruction significantly improved in the anti-LT–treated groups (p < 0.05). High-dose anti-LT or the combination of low-dose anti-LT and antihistamine significantly improved allergy symptoms compared with no treatment, low-dose anti-LT, or antihistamine alone (p < 0.05). Furthermore, anti-LT decreased NO concentration in nasal secretions (p < 0.05), regardless of the dose administered.

Conclusion: These results suggest that high-dose anti-LT alone or the combination of low-dose anti-LY and antihistamine can effectively treat allergic rhinitis.


Key words: Allergic rhinitis, anterior rhinomanometry, antihistamine, antileukotriene, asthma, cetirizine, nasal resistance, nitric oxide, zafirlukast

A llergic rhinitis is a common disease characterized by the infiltration of inflammatory cells into the nasal mucosa.1 Two of the most abundant and potent mediators are histamine and cysteiny1 leukotrienes (LTs).3,4 Histamine has long been implicated as a major mediator of allergic rhinitis, primarily causing sneezing, nasal itching, and rhinorrhea. In contrast to histamine, LTs such as LTC4 and LTD4 contribute to vascular permeability and vasodilation resulting in mucosal swelling, which causes rhinorrhea and nasal congestion.5–7 In addition, the nasal allergen challenge-induced release of cysteiny1 LTs has been correlated with allergic symptoms.8–10 Furthermore, nasal congestion in the early phase and the late phase is accompanied by a significant increase of cysteiny1 LTs in nasal lavage fluid from allergic rhinitis patients.9 Therefore, it is indicated that cysteiny1 LTs play an important role in allergic rhinitis.

Studies support the possibility that nitric oxide (NO) plays an important role in regulating nasal functions.11–14 Recent studies in rats showed that the increased vascular permeability induced by a histamine nasal challenge can be blocked by perfusion with an NO synthase (NOS) inhibitor in the nasal cavity contralateral to nasal challenge.12,13 A rabbit study showed that the nasal application of sodium nitroprusside, an NO donor, increased ciliary beat frequency in vitro and mucociliary activity in vivo.15 The same nasal application of an NO donor also has been shown to increase the mucociliary activity and blood flow in human nasal mucosa. These findings indicated that NO plays an important role in the regulation of vascular permeability, mucociliary activity, and blood flow in nasal mucosa. An elevated level of NO in nasal-exhaled air has been found in patients with allergic rhinitis; this elevation decreased after treatment with steroid nasal spray or antihistamine.17–19 However, the relationship between the NO concentration in the nasal secretion and anti-LT effect remains unknown. This study was conducted for two purposes. First, we designed a randomized trial to compare the effect of anti-LT, antihistamine, and a combination of anti-LT and antihistamine on the symptoms of allergic rhinitis and also on nasal resistance measured by active anterior rhinomanometry (AAR). Second, we investigated the concentration of nasal secretion of NO in the allergic rhinitis patients treated with anti-LT, antihistamine, or a combination of both.

MATERIALS AND METHODS

This study was approved by the Committee of Clinical Research Studies at the Veterans General Hospital-Taipei. All patients were told the aim of the study, after which each patient provided written informed consent.

Patients and Study Design

Patients eligible for this study were healthy adult men and women who had a clinical history of allergic rhinitis for at least 2 years and who tested positive only for mite allergy in the multiple allergen simultaneous test. All patients suffered from persistent, moderate to severe allergies according to the
classification of Allergic Rhinitis and Its Impact on Asthma. Patients were excluded if they had any chronic nasal diseases or if they had received corticosteroid nasal spray, oral antihistamine, oral decongestant, or oral corticosteroids in the past 3 months.

During a 7-day lead-in period, baseline nasal resistance and NO concentration of the nasal secretions were obtained and diary card assessments were performed on 120 adult allergic rhinitis patients. Then, these patients were randomly selected to receive one of the following six treatments for 4 weeks: no treatment (P group), 10 mg of cetirizine once per day (C group), 20 mg of zafirlukast once per day (Z20 group), 20 mg of zafirlukast twice per day (Z40 group), a combination of 20 mg of zafirlukast and 10 mg of cetirizine once per day (Z20+C group), or a combination of 20 mg of zafirlukast twice per day and 10 mg of cetirizine once per day (Z40+C group). After 4 weeks, the nasal resistance was measured, as well as the NO concentration in the nasal secretions, and the diary card assessments were recorded again.

Symptom Scale Score
Subjective assessment of nasal symptoms was conducted before and throughout the study; patients assessed their subjective sensations of sneezing, rhinorrhea, and nasal obstruction. Symptoms were graded on a scale of 0–10, with 0 representing no perceived symptoms and 10 representing the greatest severity of symptoms imaginable. This assessment was made both at baseline and after treatment.

Measurement of Nasal Resistance
Measurements of nasal resistance were made using a Mercury Electronics NR6 rhinomanometry (Instrument Rhinomanometry NR6-2 G. M. Instruments, Ltd., U.K.) for AAR. This rhinomanometry measured the nasal flow rate during tidal breathing, while simultaneously measuring the nasopharyngeal pressure that produced the flow. Airflow was measured using a face mask with a pneumotachograph positioned at the inlet. An integral nasal cannula for measuring nasopharyngeal pressure was placed in the subject’s nasal cavity and sealed with the tape. The face mask was placed firmly on the face and the airflow was measured through the other nasal cavity. Inspiration and expiration were measured separately. AAR resistance was measured separately for each side of the nose and the total resistance was calculated by the computer program.

Collection of Nasal Secretion
A microsuction system, which was designed by the investigators, was used to collect nasal secretions. The applied pressure was 0.04 MPa (~408 cm H2O). Under the rigid scope, we put the suction into patients’ nasal cavities and aspirated all secretion in the nasal cavity. Nasal fluid was stored on ice and centrifuged for 10 minutes at 1000 × g. The supernatant was stored at −80°C until analysis. Concentrations of NO in the nasal secretions were measured using HPLC.

Measurement of NO2 and NO3 Levels
NO2 and NO3 levels in the nasal secretions were separated by a reverse-phase separation column packed with polystyrene polymer (NO-PAK, 4.6 × 50 mm; Eicom, Kyoto, Japan), and NO3 was reduced to NO2 in a reduction column packed with copper-plated cadmium filings (NO-RED; Eicom). NO2 was mixed with a Griess reagent to form purple azo dye I in a reaction coil. The separation and reduction columns and the reaction coil were placed in a column oven that was set at 35°C. The absorbance of the product dye at 540 nm was measured by a flow-through spectrophotometer (NOD-20; Eicom). The mobile phase, which was delivered by a pump at a rate of 0.33 mL/minute, was 10% methanol containing 0.15 M of NaCl/NH4Cl and 0.5 g/L of 4Na-EDTA. The Griess reagent, which was 1.25% HCl containing 5 g/L of sulfanilamide with 0.25 g/L of N-naphthylethenediamine, was delivered at a rate of 0.1 mL/minute. The contamination of NO2 and NO3 in Ringer’s solution and the reliability of the reduction column were examined in each experiment.

Data and Statistical Analysis
All results were analyzed by one-way analysis of variance, which was adjusted for multiple comparison by Duncan’s method when appropriate. The values of p < 0.05 were considered significant. All data are presented as means ± SE.

RESULTS
One hundred twenty allergic rhinitis patients were included in this study. The male-to-female ratio was 74:46, and their ages ranged from 18 to 68 years. Before treatment, the symptom score, nasal resistance, and NO concentration of nasal secretion showed no significant differences between each group. The total symptom score improved after treatment in the treated group (p < 0.05; Fig. 1A). The high-dose anti-LT alone (Z40) and the combination of anti-LT, including low- and high-dose, and antihistamine (Z20+C and Z40+C) caused better results than the low-dose anti-LT (Z20) or antihistamine (C) alone (Fig. 1A). In the C group, the symptoms of sneezing and rhinorrhea improved significantly (Fig. 1, C and D), but nasal obstruction did not improve (Fig. 1B). In the Z20 group, rhinorrhea improved, but sneezing and nasal obstruction did not (Fig. 1, B–D). All allergic symptoms, including sneezing, rhinorrhea, and nasal obstruction, were significantly reduced after Z40, Z20+C or Z40+C treatment; however, the treatment effect was similar in Z40, Z20+C, and Z40+C groups (Fig. 1, B–D).

The objective nasal resistance was measured via AAR before and after treatment. Both the P group and the C group showed no change after treatment. Nasal resistance significantly decreased in patients who received Z40, Z20+C, and Z40+C treatment. Nasal resistance did not show significant difference between the Z40, Z20+C, and Z40+C groups (Fig. 2).

The baseline nasal NOx concentration was 357 ± 65 pmol, 323 ± 74 pmol, 329 ± 51 pmol, 397 ± 98 pmol, 279 ± 53 pmol, and 412 ± 40 pmol in the P, C, Z20, Z40, Z20+C, and Z40+C groups, respectively, and there was no difference in any of the groups (Fig 3). After treatment, the NOx concentration in nasal secretions did not change in the group receiving antihistamine alone (Fig. 3). However, the concentration of NOx in nasal secretions significantly decreased after anti-LT treatment in either low or high doses. The addition of antihistamine to either low- or high-dose zafirlukast did not further reduce the concentration of NOx (Fig. 3).
DISCUSSION

Our results show that the combination of anti-LT and antihistamine improved nasal allergic symptoms significantly compared with treatments of placebo, antihistamine, or low doses of anti-LT alone. Not only did the subjective symptom score improve, but also the objective nasal resistance decreased. In addition, anti-LT decreased the NO concentration in the nasal secretions regardless of the dose administered and regardless of an additional antihistamine.

The levels of histamine and cysteinyl LTs were elevated in the nasal secretion of patients with allergic rhinitis when triggered by IgE-mediated reactions. Histamine nasal challenge induces neurological responses, such as itching and sneezing, but affects nasal congestion to a lesser degree. Therefore, LTs contribute to the pathophysiology of allergic rhinitis and potentially increase both mucus production and congestion. One recent study examined the possible advantages of a combination of anti-LT and antihistamine for asthma. That study showed that the concomitant use of loratadine and zafirlukast was significantly more effective in diminishing the response to an inhaled allergen challenge than the use of loratadine or zafirlukast alone. Both histamine and LT receptor antagonists have antiallergic and anti-inflammatory properties, including effects on mediator release and the chemoattraction of inflammatory cells. These findings suggested that administering antihistamine and LT modifiers together might result in an amplified effect in the treatment of allergic rhinitis. Our results indicated that sneezing and rhinorrhea significantly improved in C-group patients but no significant change was observed in nasal obstruction, which profoundly affects the nasal obstruction symptom score and nasal resistance. The Z20-group patients improved only in nasal obstruction, and no change was observed in rhinorrhea and sneezing. The Z40, Z20+C, and Z40+H1 groups showed significant improvement in all allergic nasal symptoms, including sneezing, rhinorrhea, and nasal obstruction, with no difference between each group. This result shows that either high-dose anti-LT or a combination of low-dose anti-LT and antihistamine has the same effect on allergic rhinitis patients. Therefore, the combination of low-dose anti-LT and antihistamine or the use of high-dose anti-LT alone is a good treatment choice for allergic rhinitis patients.

As shown in an earlier study, LTD₄ is ~5000 times more potent than histamine in inducing increased nasal airway resistance in humans. It is noteworthy that this increase is more prolonged than that induced by histamine and is similar to that induced by antigens. In recent animal studies, nasal LTD₄ challenge was shown to increase nasal airway resistance, and anti-LT can inhibit the antigen-induced increase in nasal resistance. Our results show that both a low dose or high dose of anti-LT, with or without additional antihistamine, can improve subjective nasal obstruction and objective nasal resistance. These results indicate that anti-LTs are more powerful in the improvement of nasal congestion than the new generation antihistamine in allergic rhinitis.

The relationship between NO and chronic allergic responses has been emphasized, because NO acts as a powerful mediator involved in several atopic diseases. For example,
patients with bronchial asthma have shown elevated NO levels in exhaled air. Hamid et al. reported an increased expression of NOS, which is an enzyme responsible for NO production, in bronchial epithelial cells from untreated asthmatic patients, and suggested its relevance to the pathology of asthma. In contrast to the lower airways, little is known about the function of NO in the nasal mucosa related to the allergic reaction. Kharitonov et al. recently found that nasal NO levels were significantly elevated in patients with untreated rhinitis compared with normal individuals or subjects treated with topical steroids. The previous results showed that the degree of inducible NOS expression by epithelial cells was significantly elevated in an allergic rhinitis group compared with that of the control group. However, the relationship between LTC and NO in allergic rhinitis was not clear. Our study showed that both low-dose or high-dose anti-LT treatment decreased the NO concentration in the nasal secretions of allergic rhinitis patients. Our results also showed that anti-LT significantly improves nasal obstruction and decreases nasal resistance. Therefore, the mechanism of anti-LT may improve nasal congestion by inhibiting NO formation.

CONCLUSION

High-dose anti-LT, a combination of low-dose anti-LT and antihistamine, or a combination of high-dose anti-LT and antihistamine produce the same treatment results in allergic rhinitis patients, including improved nasal allergic symptoms and nasal resistance, and decreased NO concentrations in nasal secretions. Therefore, our results indicate that two good treatment choices for allergic rhinitis patients are either the combination of low-dose anti-LT and antihistamine or the use of high-dose anti-LT alone.

REFERENCES