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Abstract

Objective. The purpose of this pilot study was to investigate the effects of HR2 on allergen-specific immunotherapy in a mouse model of allergic rhinitis.

Study Design. An in vivo study using an animal model.

Setting. Catholic Research Institutes of Medical Science.

Methods. Fifty mice were divided into 5 groups: control, allergic rhinitis (AR), immunotherapy (IT), immunotherapy with HR2 agonist (HI), and immunotherapy with HR2 antagonist (HB). All mice except for the control group were sensitized with ovalbumin (OVA). After 1 week, mice in the IT, HI, and HB groups underwent immunotherapy by intradermal injections of OVA. During immunotherapy, the HI group was injected with HR2 agonist, whereas the HB group was injected with HR2 antagonist. All sensitized mice were challenged with intranasal OVA. After the final challenge, allergic behavior was evaluated. Interleukin (IL)–13, interferon- γ , IL-10, and transforming growth factor (TGF)- β levels in nasal lavage fluid (NALF), as well as OVA-specific IgE levels in serum, were measured. The number of eosinophils in lamina propria was evaluated.

Results. The levels of serum OVA-specific IgE and IL-13 in NALF were significantly increased in the HB group compared with the IT group ($P < .05$). Also, the tissue eosinophil counts were higher in the HB group than in the IT group ($P < .05$).

Conclusion. HR2 antagonist impaired OVA-specific immunotherapy in mice. Although confirmation of this preliminary result is needed, these findings suggest that HR2 receptors may have inhibitory effects on immune tolerance. The authors suggest that application of this property could enhance the efficiency of allergen-specific immunotherapy.

Keywords

allergic rhinitis, immunotherapy, histamine H2 receptor

Allergic rhinitis is a symptomatic disorder of the nose that is induced after allergen exposure by IgE-mediated inflammation and is characterized by 1 or more symptoms, including sneezing, itching, nasal congestion, and rhinorrhea. By conservative estimate, allergic rhinitis occurs in >500 million people worldwide.¹

Histamine has long been associated with allergic diseases and anaphylaxis. Histamine H1 receptor antagonists have been used in the treatment of allergic diseases. However, H1 antagonists do not abolish all allergic symptoms. Evidence suggests that H1-mediated mechanisms are not the only pathways by which histamine can cause inflammation of the nasal mucosa.² The pleiotropic effects of histamine are triggered by activation through 1 or several histamine membrane receptors on different cells. Four subtypes of receptors have been described: HR1, HR2, HR3, and HR4.^{3,4}

All 4 histamine receptors have been detected in the nasal mucosa, with higher levels of HR1 and HR2 in atopic individuals. Nasal challenge with histamine causes several nasal symptoms. The nasal blockage, which is experienced as congestion, is thought to result from vasodilation of the nasal arterioles and capacitance vessels. Activation of sensory neurons by histamine causes sneezing, pruritus, and activation of parasympathetic reflex. Increased release of parasympathetic mediators stimulates nasal submucosal glands, which, together with the increase in vascular permeability, cause rhinorrhea. H1 and H2 antagonists, by oral or topical administration, have

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no effect on resting nasal patency, which suggests that histamine is not normally active in the nasal interstitium.²

Several studies have suggested that HR1 antagonists affect the efficacy of allergen-specific immunotherapy. One of these has shown that antihistamines might enhance allergic sensitization and reduce the efficiency of allergen-specific immunotherapy.⁵ Another study has shown that HR1 antagonists modulate the natural course of allergen-specific immune responses and affect the expression of histamine receptors and cytokine production by allergen-specific T cells.⁶ HR2 also is known to affect peripheral T cell tolerance. Histamine via HR2 decreases the production of interleukin (IL)-4 and IL-13 and increases production of IL-10.⁷ It is also known to enhance transforming growth factor (TGF)- β 1-mediated suppression of Th2 responses. This effect is mediated by HR2 that is expressed on Th2 cells.⁸ However, they were almost all conducted in vitro or ex vivo studies, and few in vivo studies have examined the effects of HR2 on T cell tolerance.

We hypothesized that HR2 agonist might enhance tolerance induction, and HR2 antagonist might have the opposite effect. We expected that variables representing allergic inflammation, such as serum ovalbumin (OVA)-specific IgE, IL-13 in nasal lavage fluid (NALF), serum eosinophil counts, and mucosal eosinophil counts, would be decreased with administration of HR2 agonist. Variables for tolerance, IL-10 and TGF- β in NALF, also were expected to decrease with administration of HR2 antagonist. The purpose of this study was to obtain a preliminary assessment of the effect of HR2 on allergen-specific immunotherapy using a mouse model of allergic rhinitis by administration of HR2 agonists or antagonists.

Materials and Methods

Experimental Animals

Six-week-old healthy female BALB/c mice were used in this study. The experiment was performed with the approval of the Institutional Animal Care and Use Committee at the Catholic University of Korea.

Induction of Allergic Rhinitis Model, OVA-Specific Immunotherapy, and Administration of HR2 Agonist or Antagonist

Fifty mice were randomized to 1 of 5 groups of 10 each: control, allergic rhinitis (AR), immunotherapy (IT), immunotherapy with HR2 agonist (HI), and immunotherapy with HR2 antagonist (HB). On days 0, 7, and 14, all mice except for the control group were sensitized by intraperitoneal injection of 25 μ g OVA (grade V; Sigma, St Louis, Missouri) and 500 μ g aluminum hydroxide (Aldrich, Milwaukee, Wisconsin). After 1 week, mice in the IT, HI, and HB groups underwent immunotherapy,⁹ during which they received intradermal injections of 1 mg OVA 3 times at 3-day intervals. Mice in the IT group underwent only immunotherapy. In parallel with immunotherapy, mice in the HI group were treated with the HR2 agonist tolazoline (Sigma) at a dose of 50 mg/kg/d by intraperitoneal injection, whereas mice in the HB group were treated with the HR2 antagonist ranitidine (Sigma) at a dose

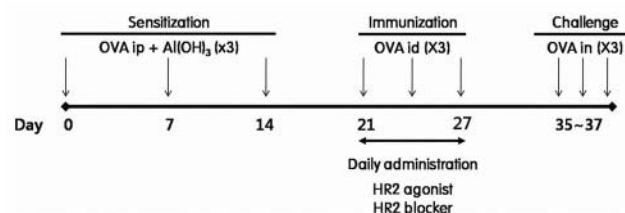


Figure 1. Schematic representation of the immunization and oral tolerance protocol. Al(OH)₃, aluminum hydroxide; HR, histamine receptor; id, intradermal injection; in, intranasal challenge; ip, intraperitoneal injection; OVA, ovalbumin.

of 100 mg/kg/d by intraperitoneal injection. Mice in the AR group, an untreated comparison group, were only sensitized and challenged with OVA. One week after immunotherapy, all sensitized mice were challenged intranasally with 50 μ g OVA for 3 consecutive days. The control group received phosphate-buffered saline (PBS) intranasally instead of OVA. We observed allergic behavior of the mice after final allergen challenge. Twenty-four hours after final allergen challenge, we obtained serum, NALF, and nasal mucosa tissue for evaluation of serum OVA-specific IgE, cytokine in NALF, and tissue eosinophil counts (**Figure 1**).

Evaluation of Allergic Behavior Induced After Allergen Challenge

The number of sneezing and nose-rubbing motions during 15 minutes after the final allergen challenge was recorded and compared between the experimental groups by blinded observers.

Nasal Lavage Fluid

Using ether anesthesia, thoracotomy was performed on the mice in each group 24 hours after the final allergen challenge. NALF was obtained after partial tracheal resection using 22-gauge catheters. The catheter was inserted into the tracheal opening in the direction of the upper airway into the nasopharynx. The nasal passages were perfused with 1 mL PBS from the choana to the nostril, and NALF was collected from the nares. NALF was centrifuged at 2000 rpm for 7 minutes at 4°C, and the supernatant was stored at -70°C. The precipitate was evaluated for cell count using a hemocytometer. The slides were prepared using a cytocentrifuge (Cytospin 2; Shandon, Runcorn, UK) stained with Diff-Quick (Dade Behring AG, Düringen, Switzerland) and evaluated for counts of macrophages, eosinophils, lymphocytes, and neutrophils by observing at least 300 cells at $\times 400$ magnification.

Nasal Mucosa Tissue Evaluation

Twenty-four hours after the final allergen challenge, the mice were killed and decapitated. The heads were fixed in 4% paraformaldehyde for 3 days at 4°C, washed in running water, decalcified for 3 days with Calci-Clear Rapid (Diagnostics, Atlanta, Georgia) at room temperature, dehydrated with serially concentrated alcohol, and embedded in paraffin blocks.

The blocks were sliced into 4- μ m-thick sections and stained with hematoxylin and eosin to evaluate general morphology and the number of eosinophils in the lamina propria. Eosinophils were counted by light microscopy. The average number of cells was counted in 4 areas around the nasal septa. The individual who counted the eosinophils was blinded.

Cytokines in NALF and OVA-Specific IgE in Serum

To evaluate the allergic reaction with the NALF (the supernatant from each group), interferon (IFN)- γ for Th1 immune reaction and IL-13 for Th2 immune reaction were measured by enzyme-linked immunosorbent assay (ELISA; Multiplex, Millipore, Billerica, Massachusetts). Serum OVA-specific IgE level was measured with an ELISA kit (Pharmingen, San Diego, California). Also, IL-10 and TGF- β were measured with the Multiplex ELISA kit.

Statistical Analysis

All measured parameters were expressed as means $\pm$ SD. The statistical parameters observed among the study groups were analyzed with a Kruskal-Wallis analysis of variance (ANOVA) by ranks test. If there were statistical significances, the ranked parameters were compared by 1-way ANOVA and Bonferroni's multiple comparison posttest (PASW Statistics 18). $P < .05$ was considered to be statistically significant.

Results

Comparison of Allergic Behavior

The mean behavior scores, which were the total number of sneezing and nasal rubbing motions during 15 minutes after the final challenge, were 9.5 ± 1.3 in the control group, 45.8 ± 11.8 in the AR group, 29.3 ± 2.3 in the IT group, 32.0 ± 8.1 in the HI group, and 35.3 ± 12.3 in the HB group. The behavior scores were elevated in the AR compared with the IT group ($P = .011$) and HI group ($P = .014$). In the control group, the behavior scores were decreased compared with those in all other groups ($P = .000$). Other comparisons failed to show significance.

Serum OVA-Specific IgE

Serum OVA-specific IgE levels were significantly increased in the AR group (35.16 ± 10.36 AU) compared with those in the other groups ($P = .000$): the control group, IT group (10.3 ± 4.27 AU), HI group (5.3 ± 3.28 AU), and HB group (19.5 ± 7.6 AU). In the HB group, serum OVA-specific IgE levels were significantly increased compared with those in the control group ($P = .000$), IT group ($P = .001$), and HI group ($P = .000$). Other comparisons failed to show significance (**Figure 2**).

Inflammatory Cells Within NALF

Figure 3 shows inflammatory cell counts in NALF. The cell counts of each group are summarized in **Table 1**. The total cell counts were higher in the AR group compared with the control group ($P = .001$). The number of eosinophils was increased in the AR group compared with the control ($P = .000$), IT ($P = .000$), HI ($P = .000$), and HB ($P = .001$) groups.

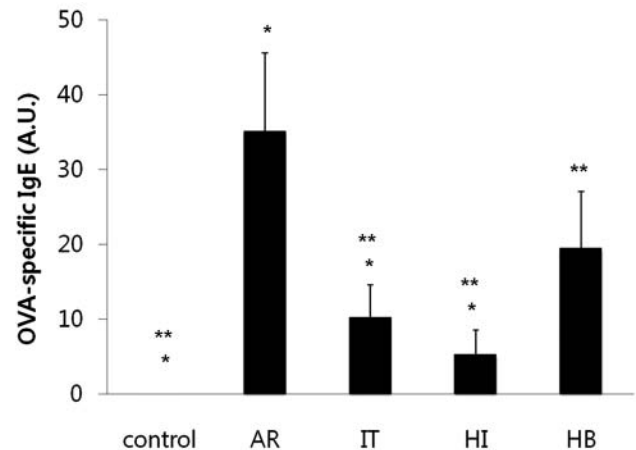


Figure 2. Serum OVA-specific IgE levels of each study group. The error bars represent standard deviation. * $P < .05$ vs the HB group. ** $P < .05$ vs the AR group. AR, allergic rhinitis; HB, immunotherapy with HR2 antagonist; HI, immunotherapy with HR2 agonist; IT, immunotherapy; OVA, ovalbumin.

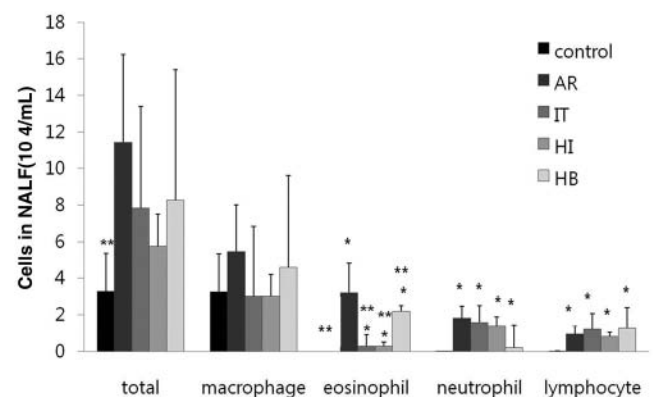


Figure 3. Inflammatory cell counts in NALF. The error bars represent standard deviation. * $P < .05$ vs the control group. ** $P < .05$ vs the AR group. AR, allergic rhinitis; HB, immunotherapy with HR2 antagonist; HI, immunotherapy with HR2 agonist; IT, immunotherapy; NALF, nasal lavage fluid.

The number of eosinophils was decreased in the control group compared with the IT ($P = .000$), HI ($P = .000$), and HB groups ($P = .000$). The number of neutrophils was decreased in the control group compared with the AR ($P = .000$), IT ($P = .001$), HI ($P = .014$), and HB groups ($P = .001$). The number of lymphocytes was also decreased in the control group compared with the AR ($P = .000$), IT ($P = .008$), HI ($P = .000$), and HB groups ($P = .004$). Other comparisons failed to show significance.

Cytokine Analysis of NALF

IFN- γ levels in NALF were 74.87 ± 6.57 pg/mL in the control group, 68.12 ± 8.62 pg/mL in the AR group, 70.85 ± 8.27 pg/mL in the IT group, 67.57 ± 5.3 pg/mL in the HI group, and 77.55 ± 6.59 pg/mL in the HB group. There was no significant difference among the groups (**Figure 4A**).

Table 1. Inflammatory Cells Within Nasal Lavage Fluid (/mL)

	Total Cells	Macrophages	Eosinophils	Neutrophils	Lymphocytes
Control	$3.29 \pm 2.07 \times 10^4$	$3.26 \pm 2.07 \times 10^4$	0	$0.02 \pm 0.001 \times 10^4$	$0.02 \pm 0.01 \times 10^4$
AR	$11.44 \pm 4.81 \times 10^4$	$5.46 \pm 2.56 \times 10^4$	$3.22 \pm 1.61 \times 10^4$	$1.81 \pm 0.67 \times 10^4$	$0.95 \pm 0.44 \times 10^4$
IT	$7.85 \pm 5.54 \times 10^4$	$3.01 \pm 3.81 \times 10^4$	$0.30 \pm 0.60 \times 10^4$	$0.40 \pm 0.91 \times 10^4$	$1.23 \pm 0.84 \times 10^4$
HI	$5.75 \pm 1.75 \times 10^4$	$3.02 \pm 1.20 \times 10^4$	$0.28 \pm 0.24 \times 10^4$	$1.38 \pm 0.51 \times 10^4$	$0.84 \pm 0.23 \times 10^4$
HB	$8.28 \pm 7.14 \times 10^4$	$4.59 \pm 2.83 \times 10^4$	$2.19 \pm 0.31 \times 10^4$	$0.22 \pm 1.20 \times 10^4$	$1.27 \pm 1.11 \times 10^4$

Abbreviations: AR, allergic rhinitis; HB, immunotherapy with HR2 antagonist; HI, immunotherapy with HR2 agonist; IT, immunotherapy.

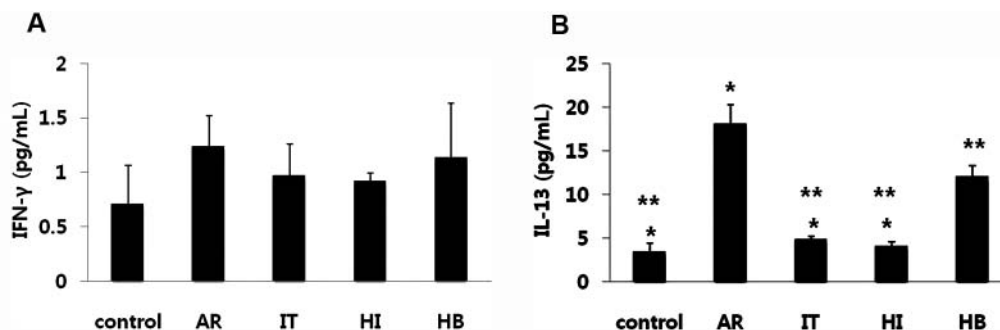


Figure 4. Cytokine levels in NALF in each study group. (A) Interferon (IFN)- γ and (B) interleukin (IL)-13 β . The error bars represent standard deviation. * $P < .05$ vs the HB group. ** $P < .05$ vs the AR group. AR, allergic rhinitis; HB, immunotherapy with HR2 antagonist; HI, immunotherapy with HR2 agonist; IT, immunotherapy; NALF, nasal lavage fluid.

IL-13 level in NALF was 35.43 ± 12.63 pg/mL in the control group, 29.12 ± 6.51 pg/mL in the AR group, 34.1 ± 10.04 pg/mL in the IT group, 31.72 ± 15.58 pg/mL in the HI group, and 43.25 ± 9.96 pg/mL in the HB group. The level of IL-13 in the AR group was higher than that in the other groups except the HB group ($P = .000$). The level of IL-13 in the HB group was higher than that in the control ($P = .000$), IT ($P = .045$), and HI groups ($P = .01$). Other comparisons failed to show significance (**Figure 4B**).

IL-10 level in NALF was 22.18 ± 2.10 pg/mL in the control group, 22.06 ± 2.59 pg/mL in the AR group, 21 ± 2.21 pg/mL in the IT group, 21.88 ± 2.86 pg/mL in the HI group, and 25.15 ± 3.81 pg/mL in the HB group. There was no significant difference among the groups.

TGF- β level in NALF was 5.01 ± 1.16 pg/mL in the control group, 4.75 ± 0.75 pg/mL in the AR group, 5.1 ± 0.73 pg/mL in the IT group, 5.0 ± 0.97 pg/mL in the HI group, and 4.41 ± 0.56 pg/mL in the HB group. There was no significant difference among the groups.

Eosinophil Counts in the Lamina Propria

The number of eosinophils in the lamina propria was 0.1 ± 0.0 in the control group, 24.6 ± 3.5 in the AR group (**Figure 5A**), 6.8 ± 1.23 in the IT group, 5.7 ± 1.11 in the HI group (**Figure 5B**), and 9.8 ± 2.41 in the HB group (**Figure 5C**). The eosinophil count in the control group was lower than that in the other groups ($P = .000$). The AR group showed a significantly higher eosinophil count than the other groups ($P = .000$). The eosinophil counts were increased in the HB group compared with the control ($P = .000$), IT ($P = .008$), and HI groups ($P = .001$). Other comparisons failed to show significance (**Figure 5D**).

Discussion

Histamine, 2-(4-imidazole)-ethylamine, is one of the most intensely studied molecules in medicine. It is synthesized from *L*-histidine exclusively by histidine decarboxylase. Histamine is produced by various cells, including central nervous system neurons, gastric mucosa parietal cells, mast cells, basophils, and lymphocytes.¹⁰

The numerous studies that have dealt with the effect of histamine during the immune response have given rise to several apparently conflicting findings. These discrepancies might eventually be explained by the differential expression of histamine receptors (HR1, HR2, HR3, or HR4), which is easily modulated by the extracellular environment and might therefore vary with the experimental setup. All these receptors are G-protein-coupled and are either expressed ubiquitously (HR1 and HR2) or restricted to specialized cell populations (HR3 in the brain and HR4 in the hematopoietic system).¹¹

HR1 is involved in allergic diseases such as allergic rhinitis, conjunctivitis, atopic dermatitis, urticaria, asthma, and anaphylaxis. HR1 is expressed in numerous cell types, including airway and vascular smooth muscle cells, hepatocytes, chondrocytes, nerve cells, endothelial cells, and several inflammatory cells, as well as T and B lymphocytes, in which it mediates the various biological manifestations of allergic responses.¹¹ HR1 antagonists have been used in the treatment of allergic diseases for nearly 50 years.² Mizuguchi et al¹² have shown that repeated pretreatment with antihistamines before provocation with toluene-2,4-diisocyanate (TDI) suppresses nasal symptoms and upregulates HR1 and IL-4 mRNA in the nasal mucosa of TDI-sensitized rats.

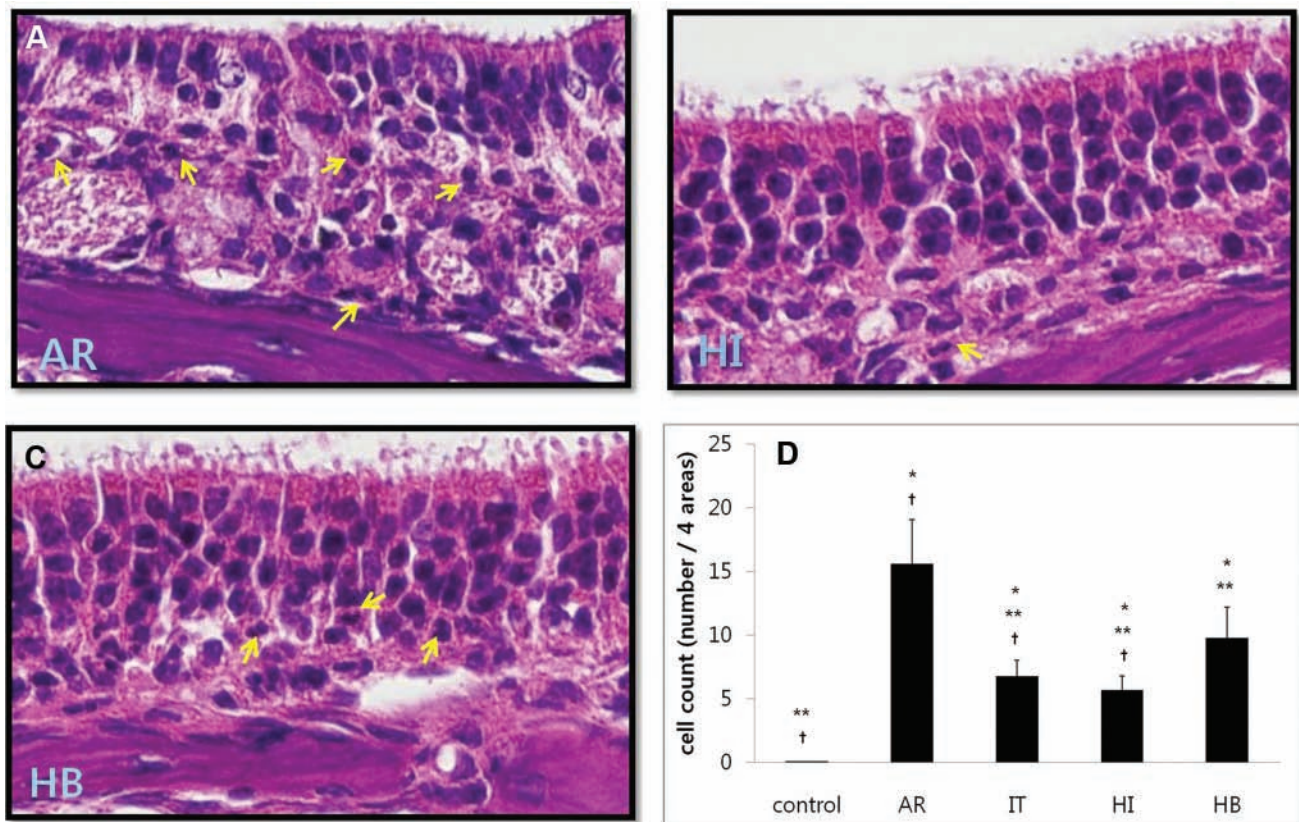


Figure 5. Photographs of hematoxylin and eosin staining ($\times 200$) of nasal mucosa tissues and graph of eosinophil count in lamina propria. (A) AR group, (B) HI group, (C) HB group. Eosinophils in nasal mucosa were significantly increased in the AR group compared with the HI or HB group. (D) Graph of eosinophil count. The yellow arrows indicate the eosinophils. * $P < .05$ vs the control group. ** $P < .05$ vs the AR group. † $P < .05$ vs the HB group. AR, allergic rhinitis; HB, immunotherapy with HR2 antagonist; HI, immunotherapy with HR2 agonist; IT, immunotherapy.

HR2 is expressed in various cell types, similarly to HR1. HR2 is mostly involved in suppressive activities of histamine, whereas positive effects are mediated through HR1. Although initially thought to regulate a limited number of activities such as heart contraction and gastric acid secretion, it is now clear that various regulatory functions of histamine during cell proliferation, differentiation, and immune response are exerted through HR2 activation.¹¹

Dijk et al¹³ have shown that tolazoline, a typical HR2 agonist, enhances delayed hypersensitivity in mice. They have also demonstrated that the IgM response is inhibited, whereas the IgG response is stimulated. These effects can be explained by assuming that suppressor T cells become more sensitive to antigen.

In 1987, Sahasrabudhe et al¹⁴ discovered that cimetidine (an HR2 antagonist) selectively inhibited the function of antigen-specific, afferent-acting suppressor T cells in mice. They suggested that cimetidine might be a useful adjunct in the immunotherapy of tumors because it can inhibit suppressor T cell function without adverse sensitization and elicitation.

Nielsen¹⁵ reviewed HR2 antagonists as immunomodulators and found that the beneficial effects of HR2 antagonists as adjuvant drugs in reducing trauma-, blood transfusion-, and sepsis-induced immunosuppression have led to research into combination treatment regimens in major surgery, particularly in patients who are undergoing surgery for malignant disease.

Flamand et al¹⁶ have reported that histamine inhibits leukotriene biosynthesis in human neutrophils. This suppressive effect of histamine on leukotriene biosynthesis is abrogated by HR2 antagonists. As a result, these authors suggested that histamine plays a dual role in the regulation of inflammation.

Meiler et al⁷ found that continuous exposure of nonallergic beekeepers to high doses of bee venom antigens induces diminished T cell-related cutaneous late-phase swelling to bee stings, in parallel with suppressed allergen-specific T cell proliferation and Th1 and Th2 cytokine secretion. After multiple bee stings, venom antigen-specific Th1 and Th2 cells show a switch toward IL-10-secreting type 1 T regulatory cells. When HR2 is upregulated on specific Th2 cells, it displays a dual effect by directly suppressing allergen-stimulated T cells and increasing IL-10 production.

In view of these results, we aimed to establish the effect of HR2 on immunotherapy using an in vivo mouse model of allergic rhinitis. We created a mouse model of allergic rhinitis that was specific to OVA and induced tolerance through OVA-specific immunotherapy. We administered HR2 agonist or antagonist to establish the direct effects on immunotherapy. Serum OVA-specific IgE was higher in the HB group than in the IT and HI groups. In NALF, IL-13 was significantly increased in the HB group compared with the IT or HI groups. Also, the number of tissue eosinophils was greater in the HB

group than in the IT and HI groups. According to these results, we found that HR2 antagonist had a suppressive effect on OVA-specific immunotherapy in this pilot study with an allergic mouse model. We hypothesized that HR2 agonist might enhance the efficacy of immunotherapy, but they had little such impact. We suggest that this was because we could not administer HR2 agonist at a sufficient dose.

Conclusions

Our study demonstrated that administration of HR2 blocker impaired OVA-specific immunotherapy in a model of allergic mouse. However, there was no significant difference in immune tolerance between the IT and HI groups. To strengthen our conclusion, a study with a larger number of mice might be needed. Further studies also might be required to demonstrate the particular features of HR2 and regulatory T cells that are involved in allergen-specific immunotherapy.

Author Contributions

Ji-Hyeon Shin, analysis and presentation; **Byung-Guk Kim**, analysis; **Sung Won Kim**, analysis; **Jin-Hee Cho**, analysis; **Yong Jin Park**, analysis; **Soo Whan Kim**, design, conduct, analysis, and presentation.

Disclosures

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