

Effect of pretreatment with fexofenadine on the safety of immunotherapy in patients with allergic rhinitis

Ohashi Yoshihiro, MD*; Nakai Yoshinori, MD†; and Murata Kiyotaka, MD‡

Background: Allergen-specific immunotherapy, although not a cure, remains the only treatment available that can alter the natural course of an allergic disease. However, the risk of allergen specific immunotherapy-related systemic reactions (SRs), reported to occur in approximately 1% to 14% of patients and which can range from mild to fatal in seriousness, represents a barrier to implementing this unique and effective treatment option.

Objective: To explore the possibility that pretreatment with the H₁-antihistamine fexofenadine could prevent the occurrence of severe SRs induced by immunotherapy in Japanese patients with allergic rhinitis.

Methods: In this open-label, multicenter study, 134 patients receiving immunotherapy for allergic rhinitis were randomized 1:1 to a group receiving pretreatment with fexofenadine hydrochloride (60 mg) 2 hours before immunization injection (n = 67) or to a control group receiving no pretreatment (n = 67). Patients were further grouped into those who received cedar pollen immunotherapy and those who received dust mite immunotherapy.

Results: Pretreatment with fexofenadine 2 hours before immunotherapy significantly reduced the occurrence of severe SRs ($P = .03$), significantly increased the proportion of patients receiving cedar pollen immunotherapy who achieved the target maintenance dose (TMD) ($P = .03$), and significantly reduced the length of time to attain the TMD ($P = .047$ and $P = .003$ for patients receiving cedar pollen and dust mite immunotherapy, respectively).

Conclusions: This study suggests a novel role for fexofenadine in enhancing the safety of immunotherapy and increasing the proportion of patients achieving the TMD.

Ann Allergy Asthma Immunol. 2006;96:600–605.

INTRODUCTION

Allergen-specific immunotherapy (ASIT) involves the administration, in gradually increasing doses, of an allergen vaccine to an allergic patient to ameliorate symptoms associated with subsequent exposure to the causative allergen.¹ Although not a cure, ASIT remains the only treatment available that may alter the natural course of an allergic disease. Given the high prevalence of atopy in the general population—approximately 40% of the general population is estimated to be atopic, as defined by an increased tendency toward IgE-based sensitivity resulting in the production of specific IgE antibody to common environmental allergens²—any treatment that can relieve symptoms without causing unacceptable adverse effects should be considered a valid addition to the therapeutic armamentarium.

Unlike antihistamine therapy, ASIT is associated with a risk of systemic reactions (SRs), principally severe asthma and anaphylaxis. However, reports of such risks vary widely. One meta-analysis³ reported that approximately 20% of ASIT efficacy studies did not provide information about adverse effects but that of those that did, 80% reported some systemic

adverse effects, the mean rate of which was 14%. Although most reactions were mild, a few life-threatening reactions occurred.³ However, 2 more recent prospective studies reported that only 3.7%⁴ and 1.08%⁵ of patients experienced one or more SRs, none of which was fatal.

Some patients are more likely than others to experience SRs as a result of immunotherapy. For example, in the study by Moreno et al,⁴ patients with asthma and those allergic to dust mites were more likely to experience SRs than the rest of the patient population studied, although this was not found to be statistically significant. However, Ohashi et al⁶ reported that the incidence of SRs in patients with high levels of serum IgE (>1,000 U/mL) and asthma or atopic dermatitis was 66.67% compared with only 1.64% for patients without these risk factors. However, the identification of risk factors alone cannot predict how an individual patient will respond to treatment: although the risk is miniscule, several deaths have been attributed to ASIT. For example, the UK Committee on the Safety of Medicines reported in 1986 that between 1957 and 1986, approximately 1.5 million courses of treatment were given, during which time there were 29 deaths attributed to ASIT.⁷

Despite fears about safety, ASIT has been used to treat allergic diseases caused by inhalant allergens and membrane-winged insect (Hymenoptera) venoms for more than 90 years. Indeed, venom immunotherapy is accepted as the standard of care for Hymenoptera-induced systemic allergic reactions.⁸

* Ishikiriseiki Hospital, Osaka, Japan.

† Kinki University Nara Hospital, Ikoma-city, Japan.

‡ Kinki University Hospital, Osaka, Japan.

Received for publication January 4, 2005.

Accepted for publication in revised form September 27, 2005.

Allergen-specific immunotherapy can improve the symptoms associated with seasonal or perennial allergic rhinitis (AR) and asthma.¹ An analysis of 43 double-blind, placebo-controlled studies of subcutaneous ASIT revealed that the treatment resulted in a mean reduction in allergic symptoms of 45%.³ This result is impressive when put in the context of the symptom relief obtained with other therapies: it is equivalent to, or even better than, the efficacy obtained with most antiallergic drugs.³

In addition to providing symptom relief, subcutaneous ASIT is known to confer long-term protection after treatment cessation.⁹⁻¹³ For example, Durham et al¹³ undertook a double-blind, placebo-controlled trial that showed that 3 to 4 years of grass pollen immunotherapy remained effective for at least 3 years after injections were discontinued. Scores for seasonal symptoms and the use of rescue antiallergic medication, which included short courses of prednisolone, remained low after the discontinuation of immunotherapy, and there was no significant difference between patients who continued immunotherapy and those who discontinued ($P = .60$); symptom scores in both treatment groups were markedly lower than those in the group that had not received immunotherapy.¹³

Allergen-specific immunotherapy has also been shown to prevent the development of further sensitivities. A prospective, nonrandomized study¹¹ in 22 children with asthma younger than 6 years, whose only sensitivity was to dust mites, demonstrated that no child receiving ASIT developed new sensitivities compared with 45% of those receiving placebo. A similar study¹⁴ indicated that ASIT can prevent the development of asthma in patients with AR. Treatment with a variety of allergens seemed to substantially reduce the risk of subsequent development of asthma during follow-up (28% of children receiving ASIT developed asthma compared with 78% of placebo-treated children).¹⁴

Despite the benefits associated with ASIT, it is recommended only in certain circumstances for patients with AR or conjunctivitis. The Allergic Rhinitis and Its Impact in Asthma guidelines reiterate the recommendations put forward in a position paper for the World Health Organization.⁸ The guidelines state that subcutaneous immunotherapy should be indicated in patients in whom antihistamines and topical drugs insufficiently control symptoms, in patients who do not wish to receive pharmacotherapy, when pharmacotherapy produces adverse effects, when the patient is concerned about long-term pharmacotherapy, and when the season is prolonged or in polysensitized patients who are exposed to several subsequent pollen seasons.

This study was prompted by the recognition that antihistamine pretreatment could improve the safety of ASIT, as has been suggested by several double-blind, placebo-controlled trials.^{15,16} The aim of the present study was to explore this hypothesis further by evaluating whether pretreatment with the H₁-antihistamine fexofenadine could prevent the occurrence of severe SRs (SSRs) induced by immunotherapy in a population of Japanese patients with AR. The newer-gener-

ation selective H₁-receptor antagonist fexofenadine was considered an appropriate choice owing to its wide therapeutic window, defining its proven efficacy in AR,^{17,18} its fast onset of action,¹⁹ and its good safety profile.^{20,21}

MATERIALS AND METHODS

Patients

A total of 134 patients receiving immunotherapy were recruited into the study between January 1, 2001, and July 31, 2001. All the patients had AR (seasonal AR alone [as a result of Japanese cedar pollenosis], perennial AR alone [as a result of sensitization to dust mites], or both). Sensitization to cedar pollen and dust mites was established at the screening visit according to methods described elsewhere.²² Patients were required to be 6 years or older, and they were excluded from the trial if they were receiving any concomitant medication. All the patients provided written informed consent, and the study was performed in accordance with Good Clinical Practice and the local authority guidelines.

Study Design

In this open-label, multicenter study, patients were randomized on a 1:1 basis (according to whether their study registration number was odd or even) to a group receiving pretreatment with fexofenadine hydrochloride (60 mg) 2 hours before immunization injection ($n = 67$) or to a control group receiving no pretreatment ($n = 67$). Investigators identified high-risk patients (conditions known to predispose patients to SRs after immunotherapy), defined as those with a history or complications of asthma or atopic dermatitis or a total IgE level of 1,000 U/mL or greater at screening.⁶

Immunotherapy was conducted once a week using the 50% to 100% escalation method; at each visit, the dose was increased by 1.5 to 2 times the previous dose. The criterion for advancing to the next dosage level was based on the duration of the wheal response. If the wheal response lasted for less than 48 hours, then the patient was provided the next concentration or dosage level. If the wheal response lasted for 48 to 72 hours, the patient continued to receive the same concentration and dosage for the next visit. If the wheal lasted for more than 72 hours, the concentration, dosage, or both were reduced by 1 level. Table 1 provides the concentration and dosage stepwise administration method used. Patients were required to stay in the clinic for at least 30 minutes after injection for the monitoring of adverse events.

Patients with perennial AR received standardized Hollister-Stier *Dermatophagoides farinae* (dust mite) extract. The target maintenance dose (TMD), the maximum dose of allergen vaccine that induces a clinically relevant effect in most patients without causing unacceptable adverse effects, was predefined as 1,000 AU/mL $\times$ 0.1 mL. Patients with seasonal AR received Torii standardized cedar pollen extract with a TMD of 2,000 JAU/mL $\times$ 0.1 mL. Patients with both pollen and dust mite allergies were treated with both immunotherapies. Injections were administered on the arm at the same place at each visit. Those who received *D. farinae* were

Table 1. Concentration and Dosage Stepwise Administration Method

Mite immunotherapy		Cedar immunotherapy	
1.0 AU/mL	0.05 mL ↓ 0.1 mL ↓ 0.2 mL ↓ 0.3 mL ↓	0.2 AU/mL	0.05 mL ↓ 0.1 mL ↓ 0.2 mL ↓ 0.3 mL ↓
10 AU/mL	0.05 mL ↓ 0.1 mL ↓ 0.2 mL ↓ 0.3 mL ↓	2.0 JAU/mL	0.05 mL ↓ 0.1 mL ↓ 0.2 mL ↓ 0.3 mL ↓
100 AU/mL	0.05 mL ↓ 0.1 mL ↓ 0.2 mL ↓ 0.3 mL ↓	20 JAU/mL	0.05 mL ↓ 0.1 mL ↓ 0.2 mL ↓ 0.3 mL ↓
1,000 AU/mL	0.05 mL ↓ 0.1 mL	200 JAU/mL	0.05 mL ↓ 0.1 mL ↓ 0.2 mL ↓ 0.3 mL ↓
		2,000 JAU/mL	0.05 mL ↓ 0.1 mL

injected in the right arm and those who received Torii cedar pollen were injected in the left arm. Patients who had both seasonal and perennial AR were injected in both arms.

The primary study end point was the incidence of SSRs, defined as symptoms due to antigen injection, such as asthma attacks and systemic anaphylaxis requiring treatment, occurring up to and including 1 month after TMD achievement. The proportion of patients achieving the TMD and the length of time required to achieve this dose were also evaluated because these variables serve as proxy measures of the effectiveness of the pretreatment in reducing the probability of adverse events occurring.

Statistical Analysis

Differences in patient baseline characteristics were analyzed using the Fisher exact test. Based on the assumption that patients were selected, randomly, from a population and allocated, randomly, to 2 independent groups (either control or fexofenadine), the nonparametric Mann-Whitney test was

used to detect treatment effects. A significance level of $P < .05$ was assumed, and it was estimated that 50 patients would need to be recruited into each arm of the study to detect statistically significant treatment effects, assuming a 10% dropout rate.

RESULTS

There were no statistically significant differences between treatment groups in patient baseline characteristics ($P \geq .23$) (Table 2). In addition, no significant differences were observed in mite specific IgE, cedar specific IgE, and total IgE levels at study entry or in the number of high-risk patients in the 2 study arms ($P \geq .58$).

Overall, the incidence of SSRs was significantly lower in the fexofenadine group (0%; 0 of 67) compared with the control group (9%; 6 of 67; $P = .03$) (Fig 1). In the control group, there were 4 cases of asthma, 2 of which were associated with laryngeal edema. These SSRs occurred on average 20.17 weeks after the first injection (range, 17–22 weeks).

Patients receiving fexofenadine before cedar pollen immunotherapy demonstrated a significantly higher TMD achievement rate compared with the control group (97% [57 of 59 patients] vs 83% [44 of 53 patients]; $P = .02$) (Fig 2). Similarly, for patients receiving fexofenadine before mite immunotherapy, the TMD achievement rate tended to be higher compared with that in the control group (91% [29 of 32 patients] vs 74% [23 of 31 patients]; $P = .11$) (Fig 3). The results demonstrated that patients in the fexofenadine and cedar pollen immunotherapy groups reached the TMD significantly sooner than those in the control group (mean $\pm$ SD, 25.7 $\pm$ 1.5 weeks vs 26.8 $\pm$ 3.1 weeks; $P = .047$) (Fig 4). The TMD was also achieved significantly faster in the patient group receiving fexofenadine and mite immunotherapy compared with the control group (mean $\pm$ SD, 18.1 $\pm$ 3.1 weeks vs 21.1 $\pm$ 4.8 weeks; $P = .003$) (Fig 5).

Table 2. Patient Baseline Characteristics

Characteristics	Control group (n = 67)	Fexofenadine group (n = 67)	P value
Age, mean $\pm$ SD, y	31.7 $\pm$ 16.1	33.9 $\pm$ 14.4	.23
Sex, M/F, No.	35/32	28/39	.23
Immunotherapy, No.			
Mites	31	32	>.99
Cedar	53	59	.17
Mites and cedar	17	24	.26
Patients at high risk for severe systemic reactions, No.	18	19	>.99
IgE, mean $\pm$ SD, IU/mL			
Mite	37.0 $\pm$ 34.6	34.6 $\pm$ 38.1	.62
Cedar	34.6 $\pm$ 33.8	38.1 $\pm$ 34.4	.58
Total	644 $\pm$ 1372	446 $\pm$ 482	.88

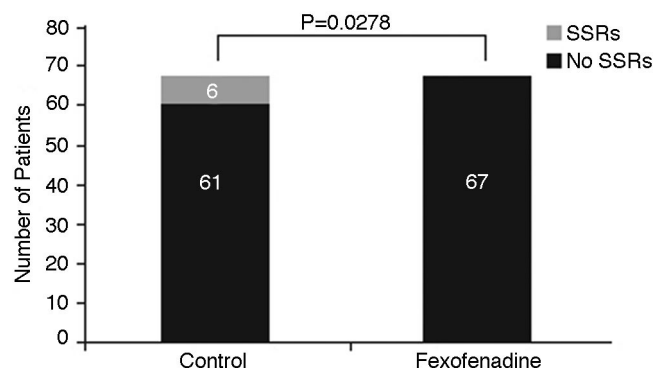


Figure 1. Number of patients with severe systemic reactions (SSRs): controls vs patients receiving pretreatment with fexofenadine hydrochloride.

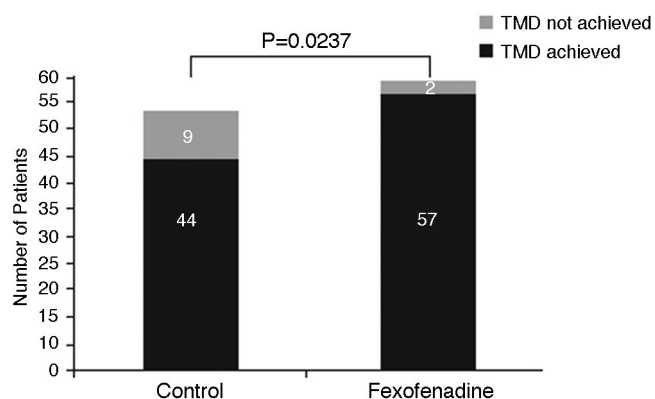


Figure 2. Number of patients receiving cedar pollen immunotherapy who achieved the target maintenance dose (TMD): controls vs patients receiving pretreatment with fexofenadine hydrochloride.

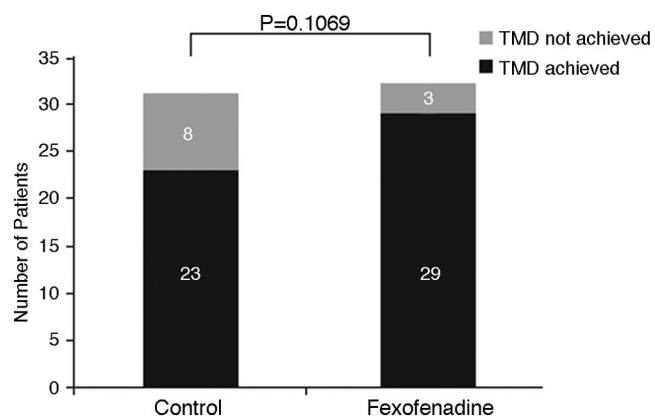


Figure 3. Number of patients receiving mite immunotherapy who achieved the target maintenance dose (TMD): controls vs patients receiving pretreatment with fexofenadine hydrochloride.

DISCUSSION

The most serious drawback associated with ASIT is the risk of SSRs; therefore, any measure that improves the safety of immunotherapy should be welcomed. This study demon-

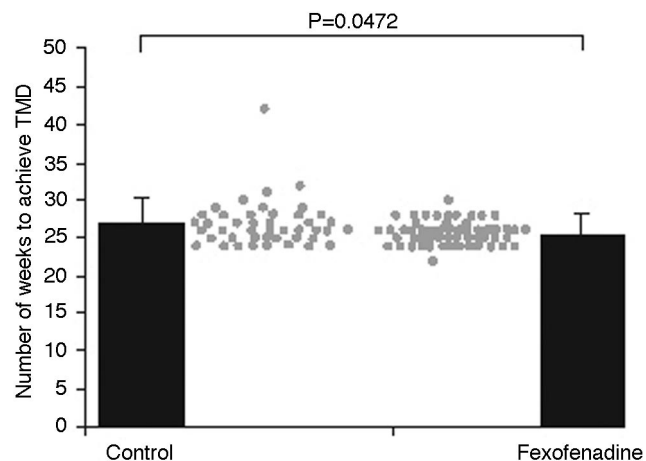


Figure 4. Weeks to achieve the target maintenance dose (TMD) in controls vs patients receiving cedar pollen immunotherapy. Error bars represent SD.

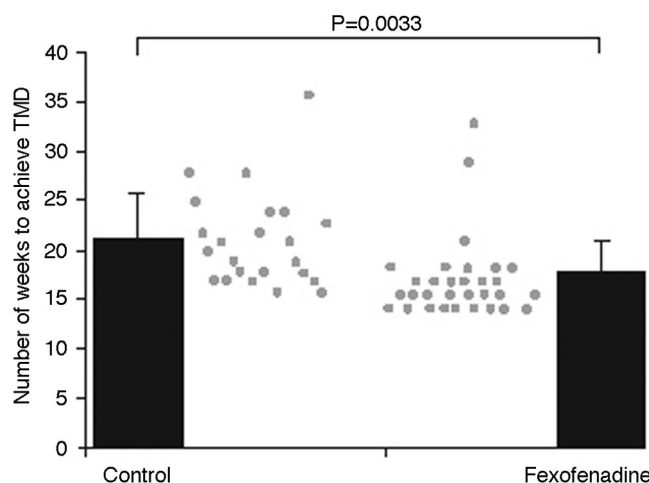


Figure 5. Weeks to achieve the target maintenance dose (TMD) in controls vs patients receiving mite immunotherapy. Error bars represent SD.

strates that pretreatment with 1 tablet of fexofenadine hydrochloride, 60 mg, 2 hours before immunotherapy significantly reduced the occurrence of SSRs, increased the proportion of patients who achieved the TMD (significantly in the case of patients receiving cedar pollen immunotherapy), and significantly reduced the length of time to attain the TMD.

These findings have several clinical implications, the first of which is that fexofenadine pretreatment enhances the safety of immunotherapy because fewer SSRs were experienced by patients who received pretreatment. Second, it could be argued that fexofenadine may promote better treatment responses to immunotherapy because more patients achieved the TMD, which is the optimum therapeutic dose. Third, there are implications of costs, resource use, and convenience linked to fexofenadine pretreatment. A patient reaching the TMD quicker will require fewer injections, thereby freeing

more resources and incurring fewer costs, and will personally experience less pain and inconvenience. Furthermore, if there is a risk associated with every immunotherapy injection, patients who receive fewer injections are less likely to experience a SR, an implication that might partially explain the improved safety associated with fexofenadine pretreatment.

This study adds weight to the existing literature supporting the use of antihistaminic pretreatment in specific immunotherapy to enhance safety. For example, a double-blind, placebo-controlled trial²³ of 22 patients (aged 6–18 years) showed that premedication with a combination of H₁- and H₂-histamine antagonists, plus an oral corticosteroid, significantly reduced the incidence of SRs during rush immunotherapy. Furthermore, recent results suggest that H₁-antihistamines, not H₂-antihistamines, confer a protective effect. In a prospective, randomized, placebo-controlled, double-blind study¹⁶ of 121 patients, pretreatment with an H₁-antihistamine (terfenadine, 120 mg), with or without an H₂-antihistamine, was shown to significantly reduce local and systemic adverse reactions to immunotherapy with Hymenoptera venom. Similarly, the second-generation H₁-antihistamine loratadine has been effective in reducing the number and severity of SRs in specific cluster immunotherapy for pollen allergy.¹⁵ In a double-blind, placebo-controlled study¹⁵ of 45 patients allergic to pollen, loratadine (10 mg) was administered 2 hours before the first injection at each visit. The median number of injections required to reach the TMD was significantly reduced in the loratadine group, as was the number of patients experiencing SRs.¹⁵

Fexofenadine hydrochloride (180 mg) reduced the adverse effects associated with ultrarush immunotherapy with honeybee venom in a double-blind, placebo-controlled trial of 57 patients.²⁴ Although systemic adverse effects were not reduced, large local reactions on day 1 of treatment were statistically significantly reduced in extent and duration with fexofenadine pretreatment, as were the symptoms of pruritus, urticaria, and angioedema.²⁴

Overall, these studies confirm that treatment with an oral H₁-antihistamine before subcutaneous immunotherapy offers some protection against SSRs. Furthermore, any antihistamine provided before treatment should not jeopardize the safety of the patient undergoing immunotherapy. The systemic safety of fexofenadine has been extensively investigated by several groups. Studies have shown that this agent has no significant effect on QTc and psychomotor function, even at doses much higher than those used in clinical practice.^{20,21,25}

Although the mechanism by which immunotherapy confers allergy protection is not fully understood, changes in T-cell reactivity are generally thought to be key to the process.²⁶ T cells have histamine receptors, and evidence exists that the expression of these receptors is altered during immunotherapy.²⁷ Therefore, the question logically arises as to whether the addition of an antihistamine could have a detrimental effect on immunotherapy, such as by binding to T-cell his-

tamine receptors and hindering the mechanism by which immunotherapy exerts its beneficial antiallergic effect.

The present study did not examine the effect of fexofenadine premedication on immunotherapy success. However, a retrospective analysis²⁶ of 47 patients who received either terfenadine or placebo before initial rush immunotherapy with honeybee venom found that premedication significantly reduced the number of mild-to-moderate systemic allergic reactions to bee sting. The authors concluded that antihistamine premedication may actually enhance the effectiveness of specific allergy immunotherapy.²⁶ Indeed, the fact that in the present study more patients receiving fexofenadine reached the TMD supports the assertion that the effects of immunotherapy could be enhanced by pretreatment, although more trials are needed to prove this hypothesis.

Immunotherapy is useful for the treatment of some cases of AR, and it is potentially lifesaving in the case of individuals at risk for death from insect stings or bites. New routes of administration of immunotherapy are currently being explored, such as nasal, sublingual, or oral immunotherapy with high-allergen doses. However, further studies are required to investigate optimum doses, appropriate patient selection, and the efficacy and safety of these novel forms of immunotherapy.⁸ It is recognized that subcutaneous immunotherapy is not without risk to the patient, and various measures have been designed to minimize the risks of allergen-specific subcutaneous immunotherapy, including the meticulous monitoring of every patient before injection by trained staff, actively involving the patient in safety monitoring, and having the capacity to treat any SR that occurs with a minimum of delay.²⁸ This study suggests that in addition to these measures, pretreatment with fexofenadine, a newer-generation antihistamine, adds to the safety and benefit of immunotherapy.

ACKNOWLEDGMENTS

We thank Drs H. Masutani, Y. Sugiura, M. Sugita, H. Okamoto, H. Sakamoto, T. Masamoto, Y. Washio, and K. Matsunaga for their participation in and contribution to the study.

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- Requests for reprints should be addressed to:
Yoshihiro Ohashi, MD
Ishikiriseiki Hospital
18–28 Yayoicho
Higashi Osaka-shi
Osaka, Japan 579-8026
E-mail: ohsymcr@circus.ocn.ne.jp