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Original article

Effect of intranasal corticosteroid on pre-onset activation of eosinophils and mast cells in experimental Japanese cedar pollinosis

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AR, allergic rhinitis; ECP, eosinophil cationic protein; FFNS, fluticasone furoate nasal spray; INS, intranasal corticosteroids; JCP, Japanese cedar pollinosis; MPI, minimal persistent inflammation

ABSTRACT

Background: Minimal persistent inflammation (MPI) contributes to hyperreactivity in allergic rhinitis. However, little is known regarding whether pre-onset activation of eosinophils and mast cells is present or not in Japanese cedar pollinosis (JCP). Furthermore, a prophylactic effect of intranasal corticosteroids on such MPI in JCP has not been investigated.
Methods: We designed a double-blinded, randomized, placebo-controlled, crossover trial. Twenty patients with JCP were examined outside the pollen season (UMIN000008410). Nasal provocation with paper discs containing extracts of Japanese cedar pollen was performed once a day for 3 consecutive days. Onset of nasal symptoms was monitored over 15 min after each provocation. The levels of eosinophil cationic protein (ECP) and tryptase in nasal secretions were examined. Fluticasone furoate nasal spray or placebo treatment was started one day before the first provocation.
Results: In the placebo group, 25% of the patients showed onset of nasal symptoms following provocation on the first day. In addition, 75% and 68% of the patients showed symptom onset on the second and third day of provocation, respectively. After the first provocation, the levels of ECP and tryptase in nasal secretions were significantly increased. These increases were seen not only in symptomatic but also in asymptomatic subjects in response to provocation, and the levels were similar between these subjects. Prophylactic treatment with fluticasone significantly suppressed the increase in nasal ECP and tryptase associated with repeated provocations.
Conclusions: These results suggest that pre-onset activation of eosinophils and mast cells is present in experimental JCP, and that prophylactic treatment with intranasal corticosteroids has the potential to control such activation.

Introduction

In allergic rhinitis (AR), minimal persistent inflammation (MPI) is characterized by an influx of inflammatory cells such as eosinophils and neutrophils into the nasal mucosa without the onset of nasal symptoms following exposure to low levels of allergen.[1] MPI was originally described after the end of symptoms in both perennial and seasonal allergic rhinitis.[2,3] It has been suggested that MPI is also present in the initial dispersion of pollen prior to onset of symptoms, which contributes to hyperreactivity and subsequently to onset of full-scale symptoms; however, the precise characterization and clinical implication of this “pre-onset” MPI remains to be elucidated.[1,3,4]

Prophylactic, in other words early interventional or initial, treatment starting immediately after pollen release or the onset of symptoms is recommended in patients who annually experience substantial symptoms of pollen-induced seasonal allergic rhinitis.[5] Placebo-controlled studies confirmed that anti-histamines, anti-leukotrienes and intranasal corticosteroids (INS) are effective for

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prophylactic treatment in pollinosis.[6–8] Of these medications, prophylactic treatment with INS has been shown to delay onset and reduce symptom severity.[1,7–10] For example, we reported that prophylactic treatment with mometasone furoate nasal spray did not induce the substantial onset of pollinosis, whereas placebo treatment did, in the relatively low pollen dispersal season in Japanese cedar pollinosis (JCP), the most prevalent seasonal allergic rhinitis in Japan.[9] In addition, we have recently demonstrated that this prophylactic treatment significantly delayed the onset of symptoms and alleviated symptom severity compared not only with placebo but also with post-onset treatment with mometasone in the relatively high pollen dispersal season.[10] One of the bases of prophylactic treatment is the control of pre-onset MPI; however, little is known regarding how INS controls pre-onset MPI.

In the present study, we sought to determine whether pre-onset activation of eosinophils and mast cells exists in experimental JCP. In addition, the efficacy of INS for this pre-onset activation was investigated. These results provide a basis for understanding the clinical implications of INS for prophylactic treatment in seasonal AR.

Methods

Patients

Twenty patients with JCP, between the ages of 22 and 52 years (mean 35.3 ± 10.4 years; 6 males and 14 females) were enrolled. All the patients had at least a 2-year history of JCP and were asymptomatic out of the pollen season. Sensitization to Japanese cedar pollen was assessed by a skin prick test. Patients were excluded from the study if they had: (a) sensitization to house dust mite assessed by a skin prick test, (b) concomitant sinonasal disease that could potentially affect the outcome of the trial (e.g., nasal polyps, rhinosinusitis, nasal septum deviation); (c) rhinitis medicamentosa and non-infectious, non-allergic rhinitis; (d) cedar pollen-specific immunotherapy; (e) sinonasal surgery including laser vaporization of inferior turbinates within 1 year; (f) medication with anti-allergic drugs including antihistamines, chromones, glucocorticoids and decongestants within 2 weeks of study initiation; (g) hypersensitivity to fluticasone furoate nasal spray; (h) systemic infection including mycosis; or (i) were pregnant and breastfeeding. Prior to the study initiation, we estimated the sample size that would be required based on the mean and standard deviation in the groups reported in our previous studies.[9,10]

Study design

The study was a single-center, double-blinded, randomized, placebo-controlled, crossover trial that was carried out in August, outside the Japanese cedar pollen season (Fig. 1). Allocation concealment was granted by the central registry and computer-generated block randomization. The control nasal provocation, followed by active allergen provocation with a 15 min interval, was given for 3 consecutive days. The allergen provocation test was performed by placing two paper discs (Torii Pharmaceutical, Tokyo, Japan) containing the Japanese cedar pollen extract that is used for skin scratch tests (14.7 μg in 5 μl per disc, Torii), to the surface of the bilateral inferior turbinates for 5 min. Control discs contained 5 μl of the control solution used for the scratch test (Torii Pharmaceutical). After 5 min, the discs with adsorbed nasal secretions were removed, placed into a 1.5 ml micro test tube (Eppendorf AG, Hamburg, Germany), and stored at −80 °C until assayed. The subjects were monitored for 15 min as to whether they showed an onset of nasal symptoms such as sneezing, itching, rhinorrhea and nasal congestion in response to nasal provocation. Fluticasone furoate nasal spray (FFNS: 55 μg per nostril once a day in the morning) or the placebo spray was administered to the subjects starting from one day prior to the first provocation. The placebo spray provided by GlaxoSmithKline K.K. had a white-colored lid and trigger. The lid and trigger of the FFNS bottle, which were initially cyan-colored, were changed to white to ensure that both FFNP and placebo spray appeared the same. This treatment was continued until the third provocation (4 days in total). Wash-out periods of 2 weeks were instituted between the treatments (Fig. 1). The study was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Rinri-1436), and is registered in UMIN (UMIN000008410). Prior to participation in the study, all patients provided written informed consent.

Measurement of nasal ECP and tryptase

The discs were soaked overnight at 4 °C in 0.8 ml of Dulbecco's phosphate buffered saline (Invitrogen, Grand Island, NY, USA) with gentle rotation. Levels of ECP and tryptase were determined by ImmunoCAP ECP and ImmunoCAP tryptase, respectively (Phadia, Uppsala, Sweden). The detection limit of the assay for ECP and tryptase was 2 ng/ml and 1 ng/ml, respectively.

Statistical analysis

Values are expressed as the median value. A non-parametric Mann–Whitney U test and Fisher's exact probability test were used to compare the data between groups, while the Wilcoxon signed rank test was used for analysis within the groups. Statistical analyses were performed using SAS (Statistical Analysis System) version 9.2, with $P < 0.0.5$ considered to be significant.

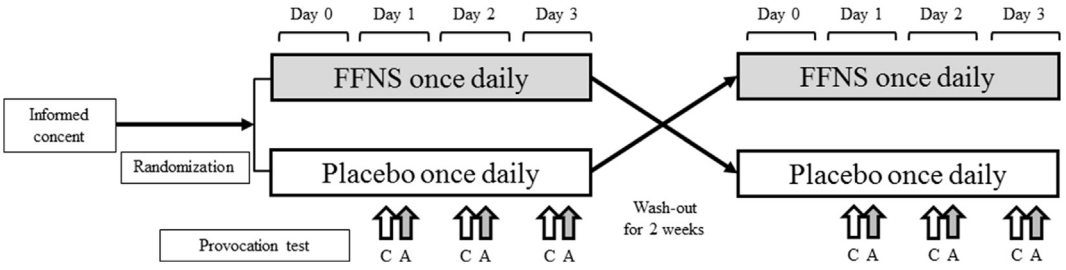

Fig. 1. Study design. Subjects received a nasal provocation test with control discs (C) followed by allergen discs (A) for 3 consecutive days. Fluticasone furoate nasal spray (FFNS) or a placebo spray was given to the subjects starting from one day prior to the first provocation. After wash-out for 2 weeks, a crossover trial was performed.