

The phosphodiesterase 4 inhibitor roflumilast is effective in the treatment of allergic rhinitis

Bernhard M. W. Schmidt, MD,^a Matthias Kusma,^a Martin Feuring, MD,^a Wolfgang E. Timmer, MD,^b Markus Neuhäuser, PhD,^b Thomas Bethke, MD,^b Boris A. Stuck, MD,^c Karl Hörmann, MD,^c and Martin Wehling, MD^a Mannheim and Konstanz, Germany

Background: The beneficial effects of phosphodiesterase 4 (PDE4) inhibitors in allergic asthma have been shown in previous preclinical and clinical studies. Because allergic rhinitis and asthma share several epidemiologic and pathophysiologic factors, PDE4 inhibitors might also be effective in allergic rhinitis.

Objective: The main objective of this study was to investigate the efficacy of oral roflumilast (500 µg/day) in allergic rhinitis. **Methods:** In a randomized, placebo-controlled, double-blinded, crossover study, 25 subjects (16 male, 9 female; median age, 28 years) with histories of allergic rhinitis but asymptomatic at screening received roflumilast (500 µg once daily) and placebo for 9 days each with a washout period of at least 14 days in between treatment periods. In each of the treatment periods, controlled intranasal allergen provocation with pollen extracts was performed daily beginning the third day of treatment, each time approximately 2 hours after study drug administration. Five and 30 minutes after each allergen provocation, rhinal airflow was measured by means of anterior rhinomanometry and the subjective symptoms obstruction, itching, and rhinorrhea were assessed by means of a standardized visual analog scale. **Results:** Rhinal airflow improved almost consistently during the 9 days of roflumilast treatment, and it was significantly higher at study day 9 on roflumilast in comparison with placebo, a result also found for itching and rhinorrhea. With respect to the subjective obstruction score, a significant difference in comparison with placebo could be demonstrated within 4 days.

Conclusion: This study shows that a PDE4 inhibitor, roflumilast, effectively controls symptoms of allergic rhinitis. Thus PDE4 inhibitors might be a future treatment option not only in allergic asthma but also in allergic rhinitis or the combination of the 2 diseases. (*J Allergy Clin Immunol* 2001;108:530-6.)

Key words: Allergic rhinitis, PDE4 inhibitors, asthma, rhinomanometry

Abbreviation used
PDE: Phosphodiesterase

Allergic rhinitis is a common disease that is estimated to affect approximately 8% to 24% of the population in industrialized countries.^{1,2} Although the disease is generally viewed as a minor nuisance, its symptoms—nasal obstruction, itching, rhinorrhea, and concomitant alteration of the eyes—generally impair the health-related quality of life in patients with either the perennial form or the seasonal form. Whereas the latter is induced mainly by natural pollen exposure, the former is triggered by various environmental allergens (eg, house dust and animal hair). On immunologic exposure, mediators such as prostaglandin D₂, leukotriene E₄, tryptase, and histamine are generated, reflecting the early allergic reaction. The subsequent allergic inflammation is mostly due to recruitment of eosinophils and metachromatic cells.³

The clinical impact of allergic rhinitis is enhanced by associated complications, such as sinusitis due to nasal obstruction, and by the rhinitis-asthma link; up to 40% of children and adolescents with allergic rhinitis also develop allergic asthma.^{4,5}

If complete allergen avoidance cannot be achieved or if immunotherapy has not been effective or is unsuitable—eg, in patients with sensitivity against multiple allergens⁶—drug therapy for allergic rhinitis becomes necessary. At present, first-line drug therapy for allergic rhinitis includes topical intranasal steroids and oral antihistamines.⁷ However, there is a longstanding discussion on the potential side effects of these medications. Long-term treatment with the available topical steroids might lead to atrophy of the rhinal mucosa and, especially in children, to systemic side effects, and some antihistaminic drugs might cause drowsiness or cardiac side effects, which are reflected by prolongation of the QT-interval. Despite the fact that the new generations of topical steroids and oral antihistamines seem to have considerably more moderate side effect profiles, the need remains for alternative drug therapies that are both safe and efficacious in allergic rhinitis.

One group of potential therapeutic agents are phosphodiesterase 4 (PDE4) inhibitors, which are currently under investigation for use in allergic asthma (for a review, see Gierbycz⁸). These drugs exert anti-inflammatory activi-

From ^athe Institute of Clinical Pharmacology, Mannheim University Hospital, Ruprecht-Karls-University Heidelberg; ^bByk Gulden Pharmaceuticals, Konstanz; and ^cthe Department of Otorhinolaryngology, Mannheim University Hospital, Ruprecht-Karls-University Heidelberg.

Received for publication January 5, 2001; revised July 2, 2001; accepted for publication July 9, 2001.

Reprint requests: Prof. Dr. Martin Wehling, Institute of Clinical Pharmacology, Mannheim University Hospital, Faculty of Clinical Medicine Mannheim, Ruprecht-Karls-University Heidelberg, Theodor-Kutzer-Ufer 1-3, D - 68167 Mannheim, Germany.

Copyright © 2001 by Mosby, Inc.

0091-6749/2001 \$35.00 + 0 1/81/118596

doi:10.1067/mai.2001.118596

ty by blocking the degradation of cyclic adenosine monophosphate in lymphocytes, eosinophils, neutrophils, and monocytes, thus leading to an attenuated release of histamine and leukotrienes as well as of several cytokines, including IL-4, IL-5, IL-10, and GM-CSF.⁹⁻¹³ These effects have been well established in vitro and in animal models of allergic asthma (for reviews, see Gierczyk et al¹⁴ and Torphy¹⁵).

One such PDE4 inhibitor currently under clinical investigation is roflumilast (3-cyclopropylmethoxy-4-difluoromethoxy-N-[3,5-di-chloropyrid-4-yl]-benzamide; Byk Gulden Pharmaceuticals, Konstanz, Germany).^{16,17} Roflumilast exerts selective anti-inflammatory activity in effector cells, such as mast cells, eosinophils, neutrophils, T lymphocytes, and macrophages, as shown in in vitro and in vivo studies. Preclinical animal models have indicated that roflumilast inhibits the inflammatory component of asthma; for example, after oral administration of roflumilast to guinea pigs challenged with ovalbumin, a marked inhibition of the specific allergic reaction could be demonstrated, as assessed by cell and protein influx into bronchoalveolar lavage liquid.^{16,17}

In phase I studies, approximately 200 subjects were exposed to oral doses of roflumilast; of these, more than 150 subjects received repeated daily doses of 500 µg/day for durations of up to 28 days. Furthermore, in phase II/III studies, more than 1600 patients with allergic asthma were exposed to roflumilast; of these, approximately 400 patients received 500 µg/day for a total duration of more than 9 months. Approximately 150 of these patients received the same dosage for more than 1 year. With respect to studies of chronic obstructive pulmonary disease, roflumilast has been administered to more than 600 patients; most of them have now been receiving roflumilast for more than 6 months, and approximately 200 of them have been receiving 500 µg/day.

A dose of 500 µg of roflumilast was found to be safe and well tolerated in healthy volunteers included in several phase I studies. In addition, higher doses of up to 5000 µg have been investigated. Given its pharmacokinetic half-life, which is approximately 10 to 15 hours, roflumilast is administered in a once-daily regimen. The fact that a simple treatment schedule improves patient compliance and thus efficacy further favors a once-daily treatment regimen over more complex schedules.

Because PDE4 inhibitors demonstrate anti-allergic and anti-inflammatory properties, they might be of benefit in the management of allergic rhinitis. We therefore conducted a controlled allergen provocation study in patients with histories of seasonal allergic rhinitis, investigating the efficacy of the new PDE4 inhibitor roflumilast.

METHODS

Overall study design

The study was a randomized, placebo-controlled, double-blinded, 2-period crossover trial. This study design allowed for comparison of the 2 treatments with each subject serving as his or her own control. To ensure controlled conditions of antigen exposure, the study was conducted during the allergen-free season, controlled allergen

challenge being performed during both treatment periods, as described below. At screening and on each study day, it was confirmed that patients were free of symptoms, including those caused by airborne allergens.

Each patient, randomly assigned to 1 of 2 sequence groups (roflumilast/placebo or placebo/roflumilast), received roflumilast and placebo for 9 days each, according to the treatment crossover design of the study; there was a washout period of at least 14 days between treatments. A washout period of 14 days was chosen to exclude a carryover effect. Because of the half-life of roflumilast (approximately 10 to 15 hours), the minimum washout period required would have been approximately 6 days (10 times the half-life); to be on the safe side, the washout period was prolonged to 14 days.

The maximum concentration of roflumilast (given as the geometric mean with 68% range) is 3.845 (3.013 to 4.907) µg/L when the subject has eaten (breakfast) and 6.517 (4.979 to 8.531) µg/L when the subject has fasted. Because the time of maximum concentration of roflumilast is approximately 2 hours, controlled intranasal allergen provocation with commercially available pollen extracts was performed on treatment days 3 through 9, each time approximately 2 hours after study drug administration. Five and 30 minutes after allergen challenge, rhinal airflow was measured by means of rhinomanometry and the subjective symptoms obstruction, itching, and rhinorrhea were assessed by means of a standardized visual analog scale, as described below. The 2 different assessment time points were chosen because of the known variability in the time course of a patient's response to allergen challenge.

Subjects

Twenty-five subjects (16 male and 9 female), each with a history of seasonal allergic rhinitis but asymptomatic at screening, were enrolled and included in the safety analysis. A total of 24 subjects (12 of each sequence) completed the study (median age, body weight, and height were 27 years, 76 kg, and 181 cm, respectively) and were available for efficacy analysis. One subject, having received 4 doses of roflumilast, was prematurely withdrawn by his own decision on day 4 of the first treatment period.

Inclusion criteria included the following: a history of seasonal allergic rhinitis (as stated by the patient); positive skin prick test results (see below); a reduction of at least 33% in mean rhinal airflow after allergen provocation, as measured by rhinomanometry; age between 18 and 45 years. Exclusion criteria included the following: any active disease or relevant abnormalities, as assessed in a prestudy examination; abnormal ear, nose, and throat status (eg, relevant septum deviation); symptoms of allergic rhinitis at screening; history of asthma attacks or severe anaphylactic reactions; any history of drug allergy; use of any medication during the 2 weeks preceding the study; topical or systemic anti-allergic medication use, including steroids or decongestive nose drops, during the 4 weeks preceding the study. Subjects were not allowed to smoke more than 10 cigarettes per day or to drink alcohol or coffee to excess (>20 g of alcohol or >5 cups of coffee per day). In addition, the following exclusion criteria were taken into account for women: no reliable contraception in the cycle before and after the study as well as during the study period (only intrauterine devices or registered hormonal contraceptives were allowed); pregnancy; lactation period.

Screening procedure and allergen provocation

Each of the subjects had a comprehensive medical examination performed within the 2 weeks before study inclusion. This screening examination consisted of the following: the taking of a medical history; physical examination, including nose and throat; 12-lead electrocardiography; body temperature recording; clinical laboratory

parameter determination; and a skin prick test through use of a standard battery of 20 common aeroallergens extracts*. In case of a positive skin prick test result (defined in comparison with the histamine and a negative control as a wheal diameter 3 mm larger than that of the negative control) to the pollen preparation, active anterior rhinomanometry was carried out to obtain a baseline rhinal flow value; this was followed by a controlled antigen exposure with commercially available pollen extracts (Allergopharma Joachim Ganzer KG).

Allergen challenge was done by spraying 2 puffs of the pollen suspension in each nostril. For antigen delivery, metered-dose sprays were used to provide 0.05 mL atomized solution per puff. The allergen concentration was 5000 standardized biological units/mL. The pollen extracts were selected individually for each subject by choosing the 1 or 2 allergens that had evoked a major reaction in the skin prick test during the screening examination. For particular subjects, the same allergens were used during the entire study. These were grass in 8, rye in 7, birch in 5, and hazel in 2 patients. Two patients received hazel and grass. Nasal congestion was objectively assessed by standardized rhinomanometry through use of commercially available equipment (Allergopharma Joachim Ganzer KG).

Rhinal airflow was determined as the sum of the values of both nostrils obtained at a pressure difference of 150 Pa. The rhinal flow values at 5 and 30 minutes after allergen provocation were averaged before further analysis. The percentage change from the predose value served as inclusion criterion. A subject was included in the study only if the rhinal flow decreased by at least 33% after allergen provocation at screening.

Study medication

Roflumilast at a dose of 500 µg once daily (2 tablets of 250 µg each) and placebo were administered in tablets of identical appearance to ensure that proper blinding was maintained.

Course of the study

In each treatment period, the study medication was administered on each of 9 consecutive days (study days 1 through 9) at approximately 8:00 AM under the supervision of the investigator. Two tablets, each containing 250 µg of roflumilast or placebo, were administered with 200 mL tap water after the subject ate a continental breakfast. Controlled antigen challenge was performed at 10:00 AM for 7 consecutive days (study days 3 through 9) in each study period by spraying 2 puffs of the pollen suspension into each nostril, as described for the screening visit. Five and 30 minutes after each allergen provocation, subjective nasal symptoms—obstruction, itching, and rhinorrhea—were evaluated and rhinomanometric measurements were performed.

The 3 subjective symptoms were assessed by means of a standardized visual analog scale (10 cm), the readings ranging from “Not in existence” to “Very strong.” Considering the severity of the symptom, the subject indicated the corresponding position on the scale, and the distance between “Not in existence” and the position indicated (in centimeters) represented the symptom score assigned (a value between 0 and 10). At each time point, the assessment of the subjective rating (both nostrils included) was done before the rhinomanometric measurements, because nasal symptoms can be temporarily influenced by the local manipulation imposed during measurement.

The safety of roflumilast was assessed by continuous monitoring of adverse events and by additional safety measurements made at a final

visit. The poststudy examination, including an ear, nose, and throat examination, was performed within 2 weeks of completion of the study.

Biostatistical methods

The primary variable for confirmative biostatistical analysis was rhinal airflow, as determined by rhinomanometry. The comparison of the rhinal airflow values was done by means of ANOVA for the 2-treatment, 2-period crossover design after logarithmic transformation. A separate ANOVA was performed for each of days 3 through 9. Treatment differences for these 7 days were tested by means of a stepwise closed testing procedure without need to adjust the α -level¹⁸; consecutive comparisons were performed beginning with day 9. If the difference was found to be significant, testing was done for day 8. This procedure was followed in reverse order until day 3. In case of a nonsignificant result, subsequent comparisons were not performed. For the sake of consistency with the multiplicative model, geometric means were calculated for rhinal airflow.

Secondary variables included the subjective nasal findings (obstruction, itching, and rhinorrhea). These variables were analyzed as described above for the rhinal flow, except that an additive model was used.¹⁹ For itching and rhinorrhea scores, the evaluation was performed separately for the time points 5 minutes and 30 minutes after allergen provocation, because itching and rhinorrhea scores were generally lower at 30 minutes than at 5 minutes (in contrast to rhinal airflow and obstruction score, for which similar values were obtained at the 2 time points). Because of their exploratory nature, no adjustment of the α -level was made for the testing of these multiple secondary variables.

The sample size of 24 subjects was chosen to provide 80% power in detecting a 20% difference in rhinal flow on roflumilast versus placebo at a significance level of 5% (2-sided), assuming an intrasubject coefficient of variation of approximately 20%, as indicated in a previous study.²⁰

Organization of the study

The study was conducted in accord with the revised Declaration of Helsinki, the German Drug Law, and the requirements of Good Clinical Practice.²¹ Ethical approval was obtained from the independent Ethics Committee of the Faculty of Clinical Medicine Mannheim of the University of Heidelberg. The clinical portion of the study was conducted at the Mannheim University Hospital, Germany, and sponsored by Byk Gulden Pharmaceuticals.

Results

Efficacy analysis

Roflumilast consistently provided greater improvement than placebo in geometric mean rhinal flow on all allergen provocation days (Fig 1). In comparison with placebo, roflumilast exhibited a statistically significant ($P = .007$) greater improvement (15%) on day 9. Because the difference on day 8 did not reach statistical significance, data from the earlier days (3-7) were not subjected to further hypothesis testing.

This finding was confirmed by the results of the subjective obstruction score (Fig 2). Roflumilast demonstrated a significant difference in comparison with placebo ($P < .05$; 2-sided) from study day 4 to study day 9. The subjective impression of symptom alleviation in comparison with placebo was highest on day 5 (with a reduction of 42% in the airway obstruction symptom score). Inasmuch as the subjective feeling of obstruction is caused by multiple factors in addition to the measured nasal flow, this

*The following allergens were used: maple, birch, early flowers, grain, grass (2 different preparations), rye, herbs, bushes, nettle, hazel, *Aspergillus fumigatus*, *Candida albicans*, *Cladosporidium*, *Penicillium notatum*, *Trichosporum*, mite (2 preparations), and animal epithelia (2 preparations; Allergopharma Joachim Ganzer KG, Reinbek, Germany).

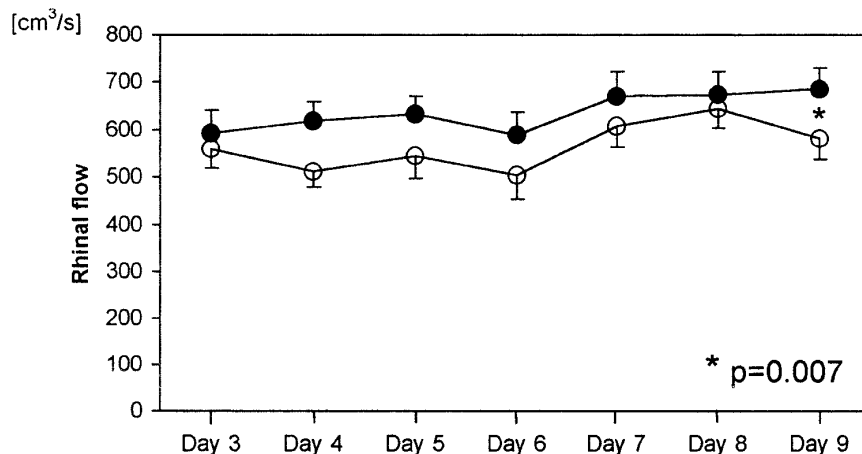


FIG 1. Time course of airway obstruction, determined objectively by rhinomanometry (geometric mean and SEM; $n = 24$) after controlled allergen challenge (5 and 30 minutes averaged) during treatment (days 3 to 9) with 500 μ g of roflumilast (●) and placebo (○).

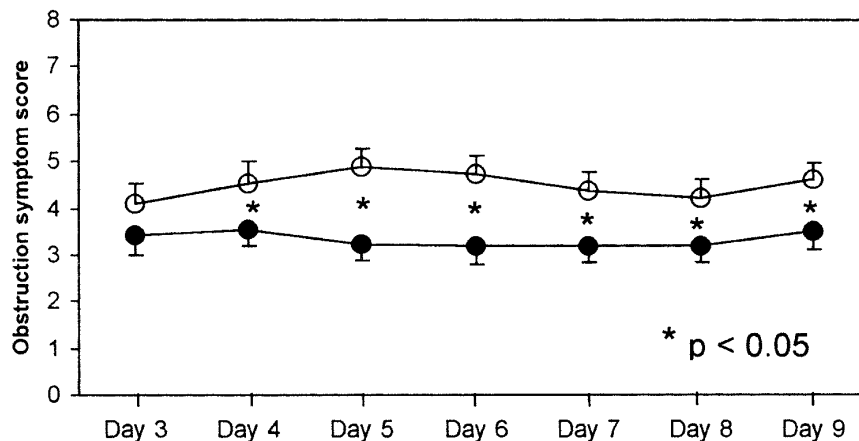


FIG 2. Time course of airway obstruction symptom score (mean and SEM; $n = 24$) after controlled allergen challenge (5 and 30 minutes averaged) during treatment (days 3 to 9) with 500 μ g of roflumilast (●) and placebo (○).

not only confirms but expands the relevance of the results of the objectively determined rhinal flow.

On all study days, the mean itching and rhinorrhea scores during roflumilast treatment were below those obtained during placebo treatment at either measuring time point. Mean itching and rhinorrhea scores observed at 5 minutes were higher than those observed at 30 minutes after allergen challenge, independently of whether the subjects received placebo or the active compound. With respect to itching, roflumilast treatment demonstrated a statistically significant difference in comparison with placebo at both time points on day 9 and at 5 minutes on all study days (Fig 3). Furthermore, with respect to rhinorrhea, roflumilast treatment demonstrated a statistically significant difference in comparison with placebo at 5 minutes on days 8 and 9 (Fig 4).

Safety

In general, treatment with roflumilast was found to be safe and well tolerated. No clinically relevant abnormalities in physical examination or clinical laboratory findings were noted. During treatment with roflumilast, headache was reported most frequently (7 of 25 subjects), followed by nausea (5 of 25) and dizziness (4 of 25). Most of the adverse events were mild; only 2 cases of headache were classified as moderate by the investigator. All of these events subsided spontaneously during continuous treatment. No serious adverse event occurred. The duration of the adverse events varied between 1 hour and 10 days. In the placebo group, only 2 adverse events were reported (dizziness and hiccups).

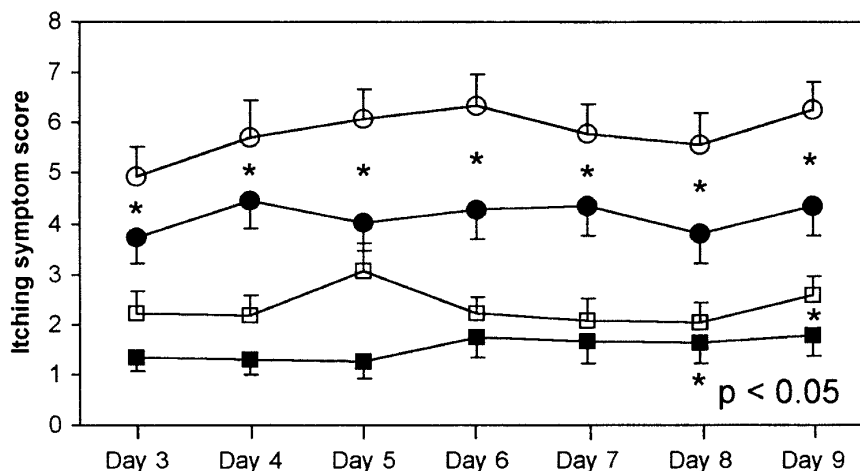


FIG 3. Time course of itching score (mean and SEM; $n = 24$) after controlled allergen challenge (separately for 5 and 30 minutes) during treatment (days 3 to 9) with 500 μ g of roflumilast (5 minutes, ●; 30 minutes, ■) and placebo (5 minutes, ○; 30 minutes, □).

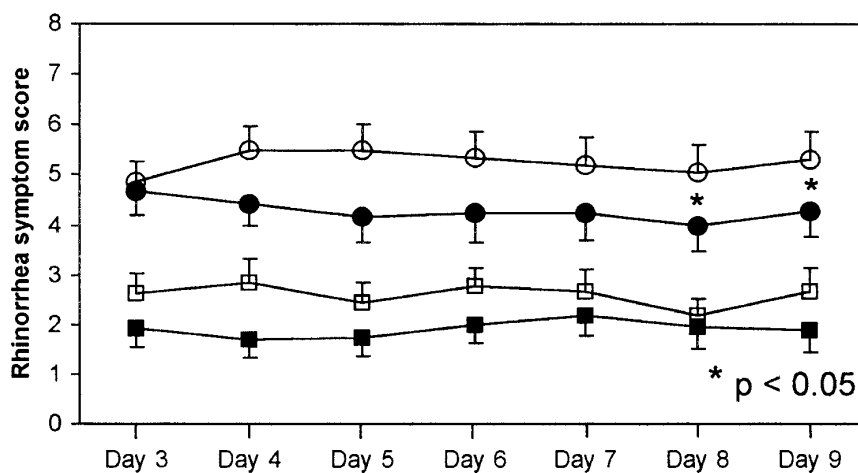


FIG 4. Time course of rhinorrhea score (mean and SEM; $n = 24$) after controlled allergen challenge (separately for 5 and 30 minutes) during treatment (days 3 to 9) with 500 μ g of roflumilast (5 minutes, ●; 30 minutes, ■) and placebo (5 minutes, ○; 30 minutes, □).

DISCUSSION

This is the first study demonstrating the efficacy of a PDE4 inhibitor in allergic rhinitis. The results clearly show that the PDE4 inhibitor roflumilast is effective in relieving the symptoms of allergic rhinitis.

This effect might be mediated by the immunomodulatory and anti-inflammatory action of specific inhibitors of the PDE4 isoenzyme, which is prevalent in white blood cells.²² Specific inhibitors of PDE4 are currently under investigation, mainly for use in chronic obstructive pulmonary disease and asthma (for review, see Giembycz⁸ and Schudt et al²³). Inhibition of PDE leads to increased intracellular cyclic adenosine monophosphate levels, which in turn suppress histamine release from mast cells and the release of several cytokines and chemokines that are involved in allergic inflammation, such as IL-1 β ,⁹ IL-

4,¹⁰ IL-5, IL-10, IL-8,¹¹ TNF α ⁹ and leukotrienes.^{12,13} In particular, the recruitment of eosinophils is decreased because of the reduced release of cytokines, especially IL-5, and probably also because of the lower expression of adhesion molecules on endothelial cells.²⁴ PDE4 inhibitors might also play a role in T_H1-mediated autoimmune diseases because of their inhibition of T-cell proliferation and a shift of the cytokine profile toward a T_H2-phenotype,²⁵ which is accompanied by the suppression of MHC-II activated immunity.²⁶ In contrast to that of the glucocorticoids, the activity of PDE4 inhibitors appears to be even more pronounced in patients with a predisposition to atopic reactions.²⁷

It was postulated that PDE4 inhibitors might be effective in the treatment of allergic rhinitis, inasmuch as the reaction causing allergic rhinitis uses, at least in part, the

immunologic pathways that are used by allergic asthma. The results of the current study support this hypothesis. An increase of the rhinomanometrically measured airflow was found as early as 3 days after treatment start, reaching statistical significance in comparison with placebo after 9 days. The difference in subjective impression of obstruction alleviation became significant on the fourth treatment day. Furthermore, statistically significant relief in comparison with placebo regarding the allergic symptoms itching and rhinorrhea was demonstrated.

Our study design might be seen as artificial. A more "natural" approach in pharmacodynamic studies is evaluation of the efficacy of a newly developed antiallergic drug in patients with allergic rhinitis during the pollen season, using natural allergen exposure.²⁸ Use of this method would have provided the advantage of evaluating nasal symptoms under the patients' usual living conditions. However, the concentration of airborne pollen grains might then have varied during the trial period, and this in turn would have influenced the study results. With controlled antigen challenge, an improved standardization of the study conditions could be achieved. To avoid additional exposure to airborne allergens, any such trial should be performed during the allergen-free season.²⁹

During the clinical development of a new antiallergic drug such as roflumilast, the first exploratory study might be conducted during the allergen-free season through use of controlled antigen delivery, inasmuch as the highly standardized conditions allow a relatively small sample size for such a "proof-of-concept" trial. In later phases, when the efficacy is to be confirmed in a larger number of patients in phase III trials, the studies should be conducted during the pollen season under the patients' usual living conditions. This is also required by agencies considering registering of the drug.

In the present study, a spray was used to deliver a defined amount of pollen extract into the nostrils. Although favorable experiences with environmental exposure units have been reported,^{30,31} the method is expensive and requires special facilities. In contrast to the environmental exposure unit, in which all subjects are exposed to the same aeroallergens, the method of intranasal allergen provocation allows the individual selection of a particular allergen to be used for provocation, an approach that we considered at least equally valid for the type of study conducted.

The rationale for performing multiple challenges in this study was to simulate the conditions of natural allergen exposure over prolonged periods; furthermore, we were thereby able to determine the onset of action of roflumilast treatment. This approach had proved to be useful in a previous trial reported by us, in which the onset of efficacy of an intranasally given steroid was determined.²⁰ In contrast to the previous investigation, a pretreatment with the trial medication was performed on the 2 days before the start of the allergen challenge, because it was hypothesized that roflumilast would already show activity on the third treatment day (preventive model); this, however, was not the case.

Because of the repeated activation, a priming effect could have occurred during the study periods. However, as seen in Fig 1, rhinal airflow rose in the placebo period on days 7 through 9 in comparison with days 3 through 6, suggesting that no priming effect occurred. It is probable that once-daily exposure to the allergen is not sufficient to induce a priming effect.

Determination of nasal air flow as a sum after allergen release to both nostrils is not a standard measure in the clinical setting. It was chosen in this study to reduce intraindividual variability, inasmuch as the effects of the physiological cyclic swelling of the nasal mucosa would be expected to average out. Moreover, the method of controlled intranasal allergen challenge and the subsequent evaluation of drug efficacy by concomitant use of anterior rhinomanometry and a symptom score had been shown to be reliable and valid in a previous trial.²⁰ It was found that the clinical efficacy of topical steroids administered as nasal sprays can be quantitatively assessed by rhinomanometry.³² The use of symptom scores is likewise a commonly accepted method.³³ Although the results of subjective and objective assessment of nasal obstruction have been shown to be significantly correlated,³⁴ there have also been reports that the rhinomanometric measurements of nasal airflow do not always reflect the patients' sensation of nasal obstruction.³⁵ Therefore, the present study evaluated the intensity of subjective nasal symptoms in parallel with rhinomanometric airflow measurements, because this complementary information might provide a more reliable assessment of nasal symptoms than the objective measurements alone. This study design was considered particularly useful for a first efficacy study on a new antiallergic compound and was thus chosen for the current trial with roflumilast.

In conclusion, this study provides evidence that oral treatment with roflumilast is an effective antiallergic therapy in allergic rhinitis. The improvement in airway obstruction seen after oral administration of the PDE4 inhibitor roflumilast was slightly inferior to the treatment effect seen in our previous study of comparable design, which evaluated the intranasal administration of the new topical steroid ciclesonide.²⁰ Direct comparison of the results of the present study with literature data obtained with other classes of drugs is hampered by substantial differences in the study designs. Several points have to be taken into consideration—eg, primary variables (objective/subjective assessment of symptoms), sample size, allergen exposure (natural/controlled), and overall statistical plan (parallel-group design/crossover design). The efficacy results of the present study are noteworthy, but given that our findings were obtained in a relatively small group of patients ($N = 24$), further studies will be required to evaluate the efficacy of roflumilast in patients with allergic rhinitis under more natural environmental and common clinical practice conditions. Moreover, comparative studies against established treatment regimens will be necessary to further specify the place that PDE4 inhibitors might take in this indication field.

REFERENCES

- Kozma CM, Sadik MK, Watrous ML. Economic outcomes for the treatment of allergic rhinitis. *Pharmacoeconomics* 1996;10:4-13.
- Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax* 1991;46:895-901.
- Pipkorn U, Karlsson G, Enerback L. The cellular response to human allergic mucosa to natural allergen exposure. *J Allergy Clin Immunol* 1988;82:1046-54.
- Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997;99:S781-S786.
- Danielsson J, Jessen M. The natural course of allergic rhinitis during 12 years of follow-up. *Allergy* 1997;52:331-4.
- Boequet J, Lockey RF, Malling H-J. WHO position paper on allergen immunotherapy: therapeutic vaccination for allergen diseases. *Allergy* 1998;53 Suppl:S1-S42.
- Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H₁ receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *Br Med J* 1998;317:1624-29.
- Giembycz MA. Phosphodiesterase 4 inhibitors and the treatment of asthma. *Drugs* 2000;59:193-212.
- Vergheze MW, McConnell RT, Strickland AB, Gooding RC, Stimpson SA, Yarnall DP, et al. Differential regulation of human monocyte-derived TNF α and IL-1 β by type IV cAMP-phosphodiesterase (cAMP-PDE) inhibitors. *J Pharmacol Exp Ther* 1995;272:1313-20.
- Souness JE, Houghton C, Sardar N, Withnall MT. Suppression of anti-CD3-induced interleukin-4 and interleukin-5 release from splenocytes of *Mesocricetus auratus* infected BALB/c mice by phosphodiesterase 4 inhibitors. *Biochem Pharmacol* 1999;58:991-9.
- Au B-T, Teixeira MM, Collins PD, Williams TJ. Effect of PDE4 inhibitors on zymosan-induced IL-8 release from human neutrophils: synergism with prostanooids and salbutamol. *Br J Pharmacol* 1998;123:1260-6.
- Denis D, Riendeau D. Phosphodiesterase 4-dependent regulation of cyclic AMP levels and leukotriene B₄ biosynthesis in human polymorphonuclear leukocytes. *Eur J Pharmacol* 1999;367:343-50.
- Jones TR, McAuliffe M, McFarlane CS, Piechuta H, Macdonald D, Rodger IW. Effects of a selective phosphodiesterase 4 inhibitor (CDP-840) in a leukotriene-dependent non-human primate model of allergic asthma. *Can J Physiol Pharmacol* 1998;76:210-7.
- Giembycz MA, Dent G, Souness JE. Theophylline and isoenzyme-selective phosphodiesterase inhibitors. In: Kay AB, editor. *Allergy and allergic diseases*. Oxford: Blackwell Scientific; 1997. p. 531-67.
- Torphy TJ. Phosphodiesterase isozymes: molecular targets for novel anti-asthmatic agents. *Am J Respir Crit Care Med* 1998;157:351-70.
- Hatzelmann A, Schudt C. Anti-inflammatory and immunomodulatory potential of the new PDE4 inhibitor roflumilast in vitro. *J Pharmacol Exp Ther* 2001;297:267-79.
- Bundschuh DS, Eltze M, Barsig J, Wollin L, Hatzelmann A, Beume R. In vivo efficacy in airway disease models of roflumilast, a novel orally active PDE4 inhibitor. *J Pharmacol Exp Ther* 2001;297:280-90.
- Bauer P. Multiple testing in clinical trials. *Stat Med* 1991;10:871-90.
- Senn S. Cross-over trials in clinical research. Chichester: John Wiley; 1993.
- Schmidt BMW, Timmer W, Georgens AC, Hilt M, Mattinger C, Wurst W, et al. The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis. *J Clin Pharmacol* 1999;39:1062-9.
- ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH Topic E6) as approved by CPMP on July 17th, 1996, and effective since January 17th, 1997; issued as CPMP/ICH/135/95, Step 5.
- Wang P, Wu P, Ohleth KM, Egan RW, Billah MM. Phosphodiesterase 4B2 is the predominant phosphodiesterase species and undergoes differential regulation of gene expression in human monocytes and neutrophils. *Mol Pharmacol* 1999;56:170-4.
- Schudt C, Gantner F, Tenor H, Hatzelmann A. Therapeutic potential of selective PDE inhibitors in asthma. *Pulm Pharmacol Ther* 1999;12:123-9.
- Blease K, Burke-Gaffney A, Hellewell PG. Modulation of cell adhesion molecule expression and function on human lung microvascular endothelial cells by inhibition of phosphodiesterase 3 and 4. *Br J Pharmacol* 1998;124:229-37.
- Bielekova B, Lincoln A, McFarland H, Martin R. Therapeutic potential of phosphodiesterase-4 and -3 inhibitors in Th1-mediated autoimmune diseases. *J Immunol* 2000;164:1117-24.
- Dousa MK, Moore SB, Ploeger NA, DeGoey SR, Dousa TP. Antagonists of cyclic nucleotide phosphodiesterase (PDE) isozymes PDE3 and PDE4 suppress lymphoblastic response to HLA class II alloantigens: a potential novel approach to preventing allograft rejection? *Clin Nephrol* 1997;47:187-9.
- Crocker IC, Ohia SE, Church MK, Townley RG. Phosphodiesterase type 4 inhibitors, but not glucocorticoids, are more potent in suppression of cytokine secretion by mononuclear cells from atopic than nonatopic donors. *J Allergy Clin Immunol* 1998;102:797-804.
- Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone propionate (200 mg) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996;98:274-82.
- Small P, Barrett D. Effects of high doses of topical steroids on both ragweed and histamine induced nasal provocation. *Ann Allergy* 1991;67:520-4.
- Day JH, Buckeridge DL, Clark RH, Briscoe MP, Phillips R. A randomized, double-blind, placebo-controlled, controlled antigen delivery study of the onset of action of aerosolized triamcinolone acetonide nasal spray in subjects with ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1996;97:1050-7.
- Kyrein HJ, Horak F, Nirnberger G, Rehn D. Efficacy of intranasally applied dimethindene maleate solution as spray in adult volunteers with symptoms of seasonal allergic rhinitis in the Vienna challenge chamber. *Arzneimittelforschung* 1996;46:794-9.
- Wiseman LR, Benfield P. Intranasal fluticasone propionate: a reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. *Drugs* 1997;53:885-907.
- Onrust SV, Lamb HM. Mometasone furoate. A review of its intranasal use in allergic rhinitis. *Drugs* 1998;56:725-45.
- Simola M, Malmberg H. Sensation of nasal airflow compared with nasal airway resistance in patients with rhinitis. *Clin Otolaryngol* 1997;22:260-2.
- Yaniv E, Hadar T, Shvero J, Raveh E. Objective and subjective nasal airflow. *Am J Otolaryngol* 1997;18:29-32.