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ALLERGY

Original article

Montelukast plus cetirizine in the prophylactic treatment of seasonal allergic rhinitis: influence on clinical symptoms and nasal allergic inflammation

Background: The aim of our study was to investigate effects of 6-week pretreatment of seasonal allergic rhinitis (AR) with cetirizine, and montelukast, alone and in combination. Antihistamine/antileukotriene treatment is effective in AR. Antihistamines may prevent AR symptoms while prophylactic activity of antileukotrienes remains unclear.
Methods: Sixty AR patients, aged 18–35 years, were randomized to receive placebo, montelukast only, cetirizine only, or montelukast plus cetirizine, 6 weeks prior and 6 weeks after the beginning of grass pollen season. Mean self-recorded in-season symptom scores and mean weekly all-symptom scores were analyzed. In 31 patients, nasal lavages were performed before treatment, and at the end of the study, i.e. 12 weeks after the treatment initiation. Eosinophil and basophil counts, eosinophil cationic protein (ECP), and mast cell tryptase (MCT) levels were evaluated in lavage samples.
Results: Combined montelukast/cetirizine pretreatment significantly reduced in-season symptom score for sneezing, eye itching, nasal itching, rhinorrhea, and congestion. Montelukast plus cetirizine were more effective than cetirizine alone in preventing eye itching, rhinorrhea, and nasal itching. Moreover, combined pretreatment with montelukast and cetirizine delayed appearance of AR symptoms. Eosinophil nasal lavage fluid counts were significantly increased during pollen season in placebo and montelukast-only groups. No differences were observed in basophil counts. The in-season ECP level was significantly increased in all groups except montelukast-plus-cetirizine group. In-season MCT levels were not increased.
Conclusion: Combined antihistamine and antileukotriene treatment started 6 weeks before the pollen season is effective in preventing AR symptoms and reduces allergic inflammation in nasal mucosa during natural allergen exposure.

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Key words: allergic inflammation; allergic rhinitis; antihistamines; antileukotrienes; prophylaxis.

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Allergic rhinitis (AR) is the most common allergic disease, affecting about 20% of the population in industrialized countries. AR is an inflammatory disease, characterized by the presence of mast cells, eosinophils (1, 2), neutrophils (3), T $CD4^+$ cells, and Langerhans cells (4) in the nasal mucosa. Coincident with the presence of inflammatory cells are increased concentrations of proinflammatory mediators: histamine (5, 6), cysteinyl leukotrienes (6, 7), mast cell tryptase (MCT) (6–8), eosinophil proteins (7–9), and Th2 cytokines (10) in nasal secretions of rhinitic subjects.

Histamine is responsible for major AR symptoms, such as rhinorrhea, nasal itching, and sneezing. Its contribution to nasal congestion is less evident, with a short lasting effect being noticeable only after challenge with high concentration (11). In contrast, leukotrienes cause mainly increase in nasal airways resistance and vascular permeability (12, 13).

Antihistamines have long been holding crucial position among agents employed in pharmacological management of AR (14). Use of the leukotriene receptor antagonist montelukast in AR has recently been approved in the United States. Data obtained by Meltzer et al. (15) show that treatment of AR with concomitant montelukast and loratadine exerts more potent inhibitory effect on AR symptoms than treatment with either drug alone. Results published by Pullerits et al. (16) suggest that intranasal steroids provide better control of nighttime AR symptoms than antihistamine and antileukotriene in combination, with comparable efficacy of both treatments with regard to daytime symptoms. Another trial (17) revealed that in patients with fall seasonal AR combination of

montelukast and loratadine was equal to loratadine alone in terms of efficacy against clinical symptoms, while a large (1302 patients) study published by Philip et al. (18) showed benefits of AR monotherapy with montelukast. Several studies involving terfenadine (19, 20), mizolastine (20), astemizole (21), azelastine and cetirizine (22) suggest that antihistamine may prevent appearance of seasonal AR symptoms when applied before natural allergen exposure period.

To date, there are no studies, which have examined the potential prophylactic properties of antileukotriene drugs in AR. We, therefore, designed a study to compare the effects of prophylactic treatment of rhinitic subjects with oral antihistamine, cetirizine and oral antileukotriene, montelukast in combination; oral antileukotriene, montelukast, alone; placebo; and oral antihistamine, cetirizine, alone. We also investigated the influence of each pretreatment protocol on selected markers of allergic inflammation in the nasal mucosa.

Methods

Study design

We conducted a double blind, parallel-group, placebo-controlled study between March and June 2002 in the city of Łódź, Poland. We studied seasonal AR patients. Approval of the Research Ethics Commission of the Medical University of Łódź had been obtained, and subjects who participated have given written informed consent. Our end-points were the daily rhonoconjunctivitis symptom score recorded during the grass pollen season, inflammatory cell count, and levels of eosinophil cationic protein (ECP) and MCT in nasal lavage fluid (NLF) during grass pollen season, after 6 weeks of prophylactic treatment followed by approximately 6 weeks of in-season treatment. The study design included seven patient visits. Schematical presentation of the study design is shown in Fig. 1. The date we decided, for the purpose of this study, to choose as the beginning of grass pollen season, the same time being the date when medication was changed in group A, was taken from the pollen calendar drawn up based on the pollen counts ascertained in the study area during previous years. Nasal lavages were performed on visits 2 and 7 in 31 patients who agreed for this procedure.

Patients were randomly assigned to one of the following treatments: group A, placebo for both cetirizine and montelukast before the expected beginning of grass pollen season (i.e. before May 15) and active cetirizine 10 mg/day plus active montelukast 10 mg/day after May 15; group B, active montelukast 10 mg/day plus placebo for cetirizine; group C, active cetirizine 10 mg/day plus placebo for montelukast; and group D, active cetirizine 10 mg/day plus active montelukast 10 mg/day throughout the study period. Patients were instructed to start taking medications on April 1, i.e. 6 weeks before the expected beginning of the grass pollen season. Treatment was provided until the end of the study period. At each visit, the daily record cards were returned and treatment and record cards for next study period were distributed.

Medication

Cetirizine (Zyrtec 10 mg, UCB Pharma, Brussels, Belgium), loratadine (Claritine 10 mg, Schering-Plough, Kenilworth, NJ, USA), and montelukast (Singulair 10 mg, MSD, Whitehouse Station, NJ, USA) were kindly provided by the respective companies. Boxes containing medication for periods between the visits were prepared by employees of the hospital pharmacy not involved in the design and performance of the study. Tablets were crushed and the powder placed in easy to swallow wafer containers. Lactose powder was used as placebo. There were two similar bags containing appropriate number of containers in each box. Bags were not labeled and boxes were labeled with patient number only. Attribution of each box to a treatment group was known solely to the hospital pharmacy employees involved in their preparation. Patients were instructed to take one container from each bag every day.

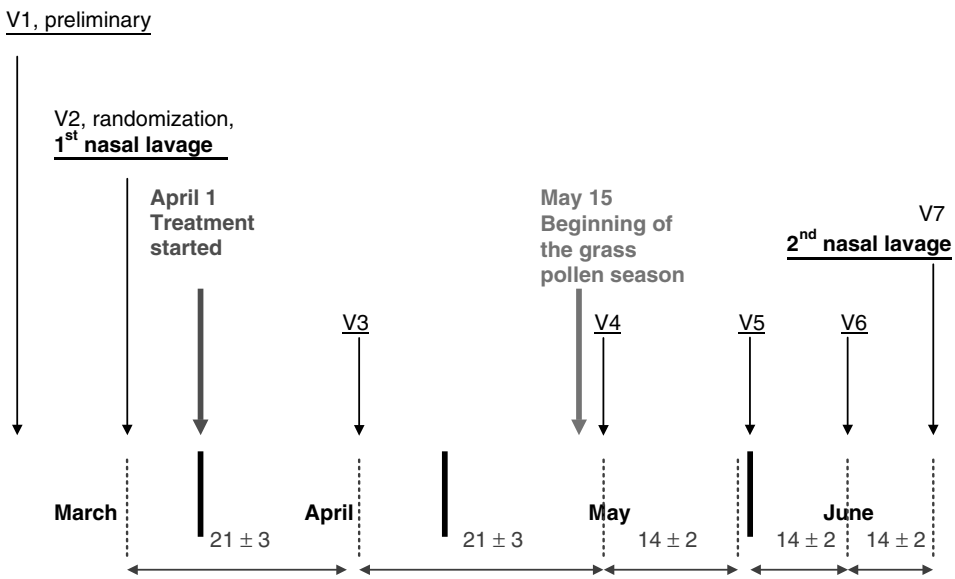

Figure 1. Study design scheme. Intervals between visits (V) given in days.

Subjects

Patients of both sexes aged 18–35 years with a history of seasonal AR symptoms for 2 years or more and positive skin prick test to a mixture of grasses or grasses/cereals allergens (Allergopharma Joachim Ganzer KG, Reinbek, Germany) were eligible for the study. Seasonal character of AR in the study participants was established on the basis of the time of occurrence of symptoms during the year. According to the classification proposed by Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop Expert Panel (23), which is now being evaluated in the general practice setting (24), most patients in our study would be described as having intermittent AR. However, in a French ARIA evaluation survey (24) about 43.7% of patients diagnosed with seasonal AR according to the traditional classification, have been classified as persistent rhinitics when the ARIA criteria were employed. Therefore, we assume that, in terms of the new classification, some of our patients had persistent AR. Patients diagnosed with bronchial asthma, having polyvalent pollen allergy, suffering from rhinitis outside the pollen season, using specific immunotherapy, or participating in another drug efficacy trial during 4-week period preceding the study were not considered eligible for inclusion. Additional exclusion criteria included electrocardiographic abnormalities (prolonged QTc interval, conduction delay), nasal septum deviation, nasal surgery within 12 months preceding the study, and any other clinically significant disorder that could increase patients' risk, influence the results or limit patients' ability to participate in the study, as judged by the investigator. Female patients had to demonstrate negative pregnancy test before inclusion and agree to use appropriate contraception during the study. Excluded medications were topical or systemic steroids, cromolyns, nonsteroidal anti-inflammatory agents, topical or systemic antihistamines, leukotriene modifiers, macrolide antibiotics, and imidazole-derived antifungal agents (ketokonazole, itrakonazole).

Sixty patients (46 men and 14 women, aged 18–35 years, mean age 24.63 ± 4.9 years) were originally randomized to treatment. Forty-eight subjects (38 men and 10 women, mean age 24.94 ± 5.12 years) completed the study.

Rhinoconjunctivitis symptom score

Symptoms of AR and conjunctivitis were assessed on a 6-point scale and recorded daily in patients' diaries. Questions concerned daytime nasal (congestion, rhinorrhea, itching, and sneezing) and eye (lacrimation, itching) symptoms. The system we designed for symptom scoring was as follows: 0, absence of symptom; 1, minimal symptom, hardly noticeable; 2, mild symptom, noticeable yet not bothersome; 3, moderate symptom, noticeable and sometimes disturbing; 4, severe symptom, disturbing most of the time; 5, very severe symptom, preventing from everyday life activities.

Nasal lavage

Nasal lavage fluid samples were obtained with the use of 'nasal pool' device described elsewhere by Greiff et al. (25). The fluid was centrifuged for 10 min at 300 ***g***. Supernatant was collected and stored at −20°C. Approximately 600 ml of fluid and cell pellet remained at the bottom of the tube.

Nasal lavage cells count

Two smears were made from one NLF sample: one stained with eosin and methylene blue for eosinophil percentage count and the other with toluidine blue for basophil percentage determination. At least 200 cells per smear were evaluated and differential count was made.

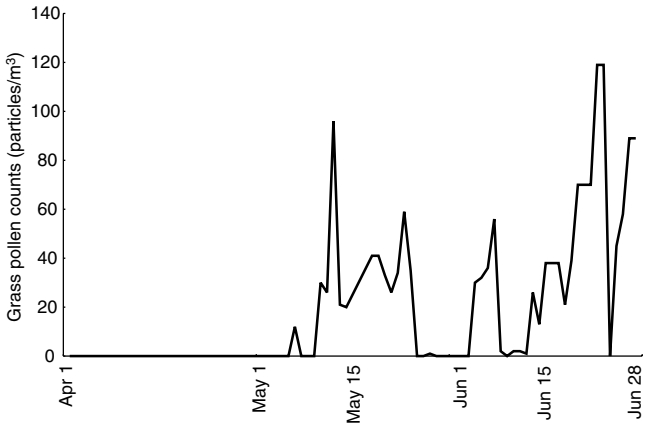

Figure 2. Grass pollen counts in the study area during the treatment period.

Eosinophil cationic protein and mast cell tryptase in nasal lavage

Concentrations of ECP and MCT in NLF were measured by using UniCap Pharmacia system (Pharmacia Diagnostics AB, Sweden). Samples were assayed according to the instructions of the manufacturer. Minimum detectable concentrations were: less than 2 μg/l for ECP and 1 μg/l for MCT.

Grass pollen counts

Grass pollen counts in the study area during the treatment period, acquired by the local aerobiology station, are presented in Fig. 2.

Statistical analysis

Values used for statistical analysis were mean daily scores for each symptom counted from data obtained between May 15 and the day of the last visit. Mean all-symptom scores during each week were counted additionally and used for analysis of the dynamics of AR clinical manifestations. The population used for statistical analysis of symptom scores comprised subjects who had been randomized to one of the treatments, and completed all preseason visits and at least one in-season visit. Cell counts and concentrations of ECP and MCT in preseason NLFs were compared with those in samples obtained at visit 7, in the last week of June.

Nonparametric methods were used for statistical evaluation. Comparison of all four pretreatment protocols was done with Kruskal–Wallis Anova, comparisons between the groups were done with Mann–Whitney *U* test, and comparisons within the groups were done with Wilcoxon's pair rank test. *P* values less than 0.05 were considered significant. Statistica 5.1 PL for Windows software (StatSoft Polska, Krakow, Poland) was employed for analyses.

Results

Patients

Of 60 patients included into the study, 11 were randomized to group A, 11 to group B, 19 to group C, and 19 to group D. Age and sex distribution of the participants in different treatment groups are shown in Table 1. Twelve patients did not complete the study. Four patients reported aggravation of symptoms and withdrew their consent, seven were lost to follow-up, and one patient took an over-the-counter antihistamine drug. No adverse event has been reported in any patient. Reasons for discontinuation are shown in Table 2.

Two patients from group A withdrew their consent at visit 5 due to persistence of symptoms and, therefore, apparent lack of efficacy of treatment. This was also the case in one patient from group B and one from group D, who declined further participation between visits 6 and 7. The patient from group C who took an over-the-counter antihistamine between visits 5 and 6 was excluded from the study due to the violation of protocol. It must, however, be mentioned that this protocol violation occurred as a result of aggravated symptoms. Of patients who failed to comply with the visits' schedule, three were lost to follow-up after visit 5 (one from group B, one from group C, and one from group D), whereas four dropped out in the preseason period (three from group C and one from group D). According to what has been mentioned in the statistical section, results obtained from the latter were not included in the analysis. Number of study participants at consecutive time points is presented in Table 3.

Symptoms

Pretreatment with cetirizine and montelukast in combination was effective in preventing most of AR symptoms. Symptoms scores (mean ± SEM) are shown in Fig. 3.

Table 1. Demographic characteristics of patients

	M/F	Age, mean ± SD (years)
Group A (placebo)	8/3	24.15 ± 5.41
Group B (MNT)	8/3	25.45 ± 4.30
Group C (CET)	15/4	23.68 ± 4.68
Group D (MNT + CET)	15/4	25.40 ± 5.34

Abbreviations: MNT, montelukast; CET, cetirizine.

Table 2. Reasons for discontinuation

	Treatment group			
Reason for discontinuation	A	B	C	D
Exacerbation of symptoms	2	1	0	1
Violation of protocol	0	0	1	0
Lost to follow-up	0	1	4	2
Total	2	2	5	3

Table 3. Number of patients participating in the study at particular time points

		In-season period		
Group	Preseason period V_1–V_4	V_5	V_6	V_7
A	11	11	9	9
B	11	11	10	9
C	19	16	14	14
D	19	18	17	16

The most significant difference in symptom score between placebo and montelukast/cetirizine pretreated patients was observed in sneezing (2.20 ± 0.30 *vs* 0.92 ± 0.15, $P = 0.0005$), eye itching (2.01 ± 0.40 *vs* 0.54 ± 0.16, $P = 0.0007$), nasal itching (1.63 ± 0.35 *vs* 0.53 ± 0.13, $P = 0.005$), and rhinorrhea (1.72 ± 0.39 *vs* 0.41 ± 0.11, $P = 0.0093$). The prophylactic effect of concomitant montelukast and cetirizine was also significant for nasal congestion (1.83 ± 0.33 *vs* 0.93 ± 0.20, $P = 0.02$). Combined montelukast and cetirizine were more effective than cetirizine alone in preventing eye itching (0.54 ± 0.16 *vs* 1.16 ± 0.19, $P = 0.0097$), rhinorrhea (0.41 ± 0.11 *vs* 0.91 ± 0.19, $P = 0.03$), and nasal itching (0.53 ± 0.13 *vs* 1.02 ± 0.19, $P = 0.04$). None of the pretreatment protocols had prophylactic effect on the intensity of lacrimation.

A week-by-week analysis of summary score of all AR symptoms is shown in Fig. 4. It revealed that combined montelukast and cetirizine pretreatment started 6 weeks before natural allergen exposure contributed to the delay of appearance of seasonal AR symptoms. At the beginning of the grass pollen season, the symptom score in montelukast/cetirizine pretreated patients was significantly lower than in any other group. In two additional time points during the pollen season (weeks 7 and 10), patients who received montelukast and cetirizine prior to allergen exposure suffered from significantly less symptoms than those in whom treatment was started on the first day of the pollen season. Moreover, in the remaining periods of the pollen season, the symptom score in montelukast/cetirizine pretreated patients was still lower, though not significantly, than in patients from other three groups.

Cellular findings

Percentage counts of eosinophils in NLF smears performed before and during pollen season are presented in Fig. 5A. In patients pretreated with cetirizine alone and cetirizine plus montelukast, the in-season mean eosinophil NLF count was not significantly higher than the preseason count. Moreover, patients who started combined montelukast plus cetirizine treatment 6 weeks before the grass pollen season had significantly lower in-season mean eosinophil counts in NLF than patients in whom such treatment was applied at the beginning of allergen exposure period (1.75 ± 0.45 *vs* 24.67 ± 5.78; $P = 0.0006$, Mann–Whitney U test).

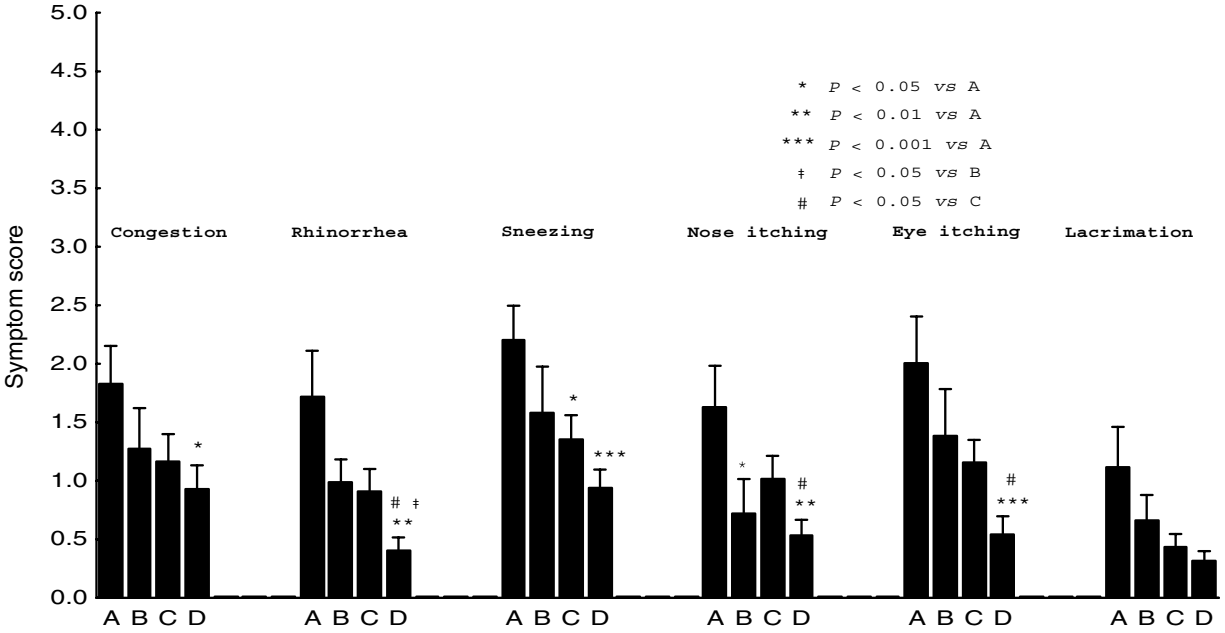

Figure 3. Symptom scores (mean ± SEM) during grass pollen season in patient pretreated during 6 weeks before natural allergen exposure period: (A) placebo, (B) montelukast 10 mg/day, (C) cetirizine 10 mg/day, and (D) montelukast 10 mg/day and cetirizine 10 mg/day.

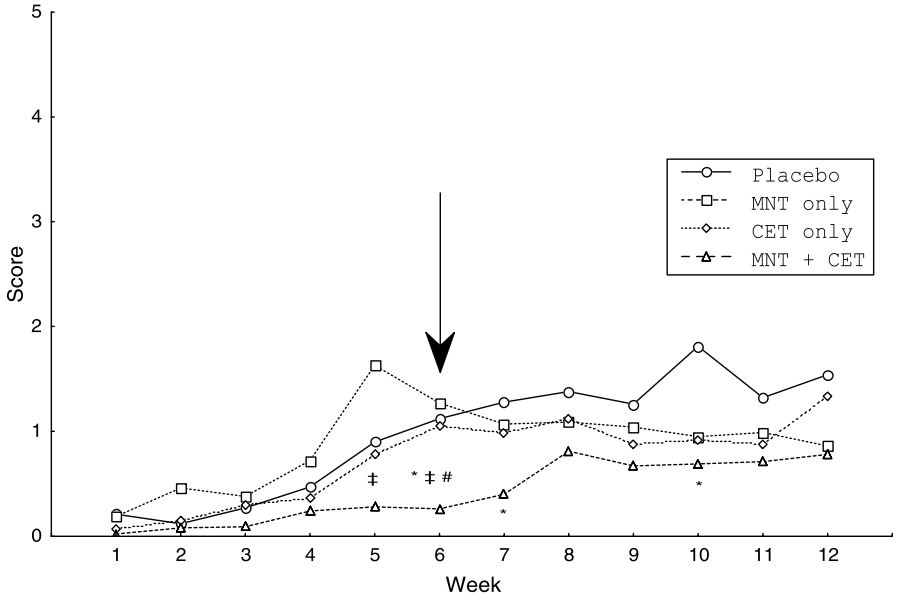

Figure 4. Summary of all-symptom score during the study period. Beginning of the grass pollen season is marked with an arrow. Time points when symptom score in MNT plus CET group was significantly lower are marked: $^{*}P < 0.05$ compared with placebo; $‡P < 0.05$ compared with MNT only; $^{\#}P < 0.05$ compared with cetirizine only. MNT, montelukast 10 mg/day; CET, cetirizine 10 mg/day.

In both preseason and in-season samples, there was not any significant difference in basophil count between treatment groups. The in-season basophil percentage counts were not significantly higher in any group, either (Fig. 5B).

Eosinophil cationic protein

In all groups, levels of ECP were elevated during the pollen season (Fig. 5C). The in-season mean ECP level was not significantly higher than the preseason level

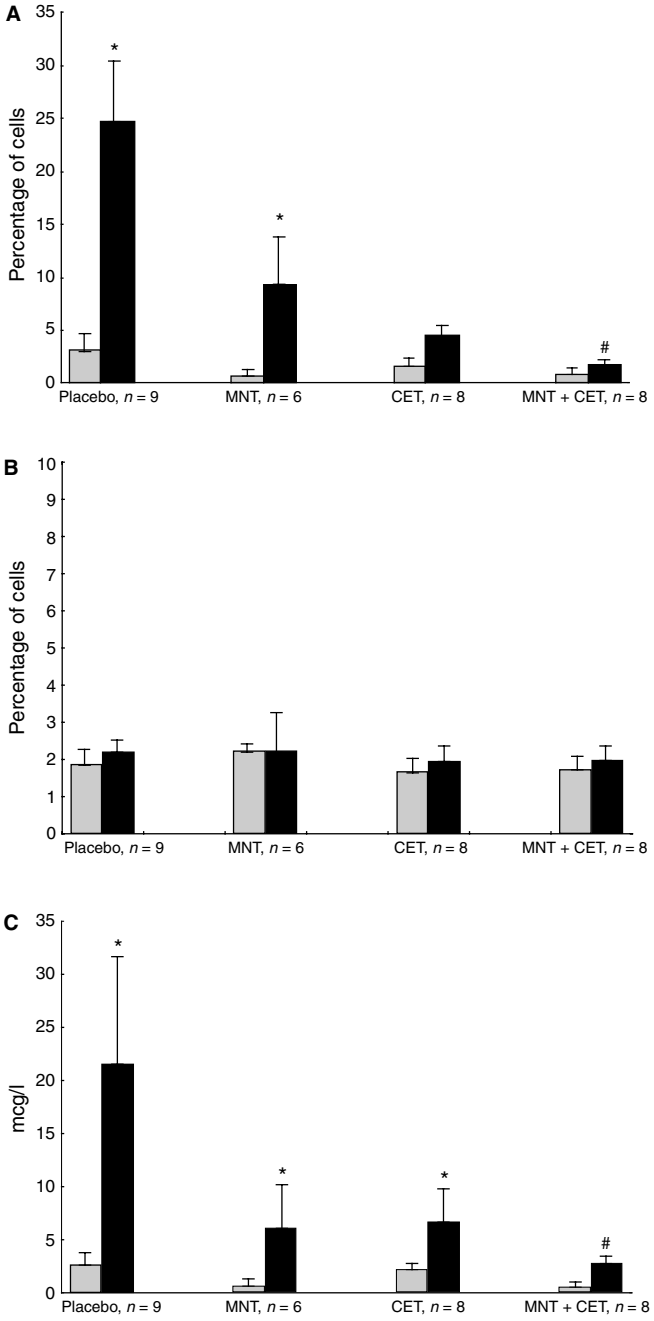

Figure 5. Mean percentage of eosinophils (panel A), basophils (panel B), and mean levels of ECP (panel C) in NLF samples obtained before (dotted bars) and during (close bars) grass pollen season. MNT, montelukast 10 mg/day; CET, cetirizine 10 mg/day.*$P < 0.05$ compared with the preseason level. $^{\#}P < 0.05$ compared with the in-season value in the placebo group.

only in patients who received combined pretreatment with montelukast and cetirizine (0.59 ± 0.39 *vs* 2.79 ± 0.75 μg/l, $P > 0.05$). The in-season ECP level in patients pretreated with montelukast plus cetirizine was significantly lower than the in-season ECP level observed in patients receiving double placebo before the pollen season (2.79 ± 0.75 *vs* 21.63 ± 10.07 μg/l; $P = 0.04$, Mann–Whitney *U* test).

Mast cell tryptase

No significant intergroup differences in MCT levels have been observed either before or during the grass pollen season. Also, a comparison within the groups showed that in-season MCT levels were not significantly elevated in any group, although higher than preseason ones (data not shown).

Discussion

In this study, we have applied a combination of antihistamine and antileukotriene agents in the prophylaxis of nose and eye allergy symptoms. We hypothesized that pretreatment with antihistamine and antileukotriene in combination will have inhibitory effect on allergic inflammation in the nasal mucosa.

Patients in whom combined 6-week pretreatment with montelukast and cetirizine had been administered, suffered significantly less from sneezing, eye and nose itching, nasal congestion, and rhinorrhea, than those in whom the treatment was started at the beginning of the pollen season. It has to be pointed out, however, that in patients from the latter group (i.e. group A) the mean symptom score during grass pollen season, although in many cases significantly higher than in the other groups, still oscillated around 2, which indicates symptoms that are noticeable but mild and not bothersome. From these results, it can neither be inferred that combined antihistamine and antileukotriene treatment of AR started at the beginning of the pollen season has no effect, nor that its efficacy is whatsoever satisfactory. Such a picture is the result of (i) large amount of data (scores recorded on a daily basis), (ii) considerable intersubject variations in response to treatment, and (iii) variations in pollen counts during the study period due to several rainy days in the area. In fact, on the days when pollen count was high many patients from group A reported more pronounced allergy symptoms than patients on other treatments.

The effect of combined prophylactic treatment on nasal congestion deserves, in our opinion, particular interest. Leukotrienes contribute to the increase of nasal resistance (12, 13). However, hitherto performed clinical studies failed to demonstrate clearly that leukotriene receptor antagonists are more effective than antihistamines in abrogating nasal blockage (26). Our results suggest that antileukotrienes are most effective against nasal blockage when applied concomitantly with an antihistamine agent.

Furthermore, combined antihistamine and antileukotriene treatment started at the beginning of the pollen season was significantly less effective with regard to most AR symptoms than any treatment started 6 weeks before

the pollen season. Clinical improvement after administration of either of the drugs is clearly visible usually within several hours. However, in our study, clinical effect was far more noticeable in those patients who received cetirizine and montelukast on a daily basis during 6 weeks before the pollen season. These results provide new insight into the mechanisms of action of both drug classes. Their cumulative effect seems to increase with the length of the treatment period. Interestingly, this phenomenon is not observed when either cetirizine or montelukast are administered alone over the same time. Studies involving larger groups of patients should address that issue.

Another important finding is that combined antihistamine and antileukotriene pretreatment may contribute to the delay of the symptoms' appearance. This was particularly visible at the beginning of the allergen exposure period, as revealed by mean weekly symptom score analysis and presented in Fig. 4.

Enumeration of inflammatory cells in nasal lavage can be a useful way of monitoring allergic inflammation in the upper airways (7, 9, 27). Both percentage of eosinophils and activity of basophils increase significantly after natural allergen exposure. Limited data are available regarding the influence of prophylactic treatment with antihistamines and leukotriene modifiers on cellular infiltration in the nasal and conjunctival mucosae. In the out-of-season study by Ciprandi et al. (19), only the total number of inflammatory cells was studied and found to be decreased in subjects taking oral terfenadine 7 days prior to conjunctival allergen provocation test. In AR patients treated with either antileukotriene alone (zafirlukast 20 mg b.i.d.) or in the combination with loratadine 3 weeks prior to the pollen season, Pullerits et al. (16, 28) did not observe inhibitory effect of those treatments on local eosinophilic inflammation. We have observed an inhibitory effect of preseason treatment of AR with cetirizine alone and cetirizine plus montelukast on the influx of eosinophils to the nasal mucosa during natural exposure to allergen. Philip et al. (18) observed significant decrease in peripheral blood eosinophil count in patients treated for 2 weeks with montelukast alone but not in those treated with antihistamine agent, loratadine. Wu et al. (29) noticed significant reduction of BAL eosinophil numbers after treatment with high-dose intravenous montelukast in the murine model of asthma. In our study, the influx of eosinophils to the mucosa was inhibited only when montelukast was applied in combination with antihistamine agent over several weeks before the pollen season. Combined antihistamine/antileukotriene treatment, which begun at the beginning of the pollen season was less effective in that matter. Lack of NLF samples collected from AR subjects who have not received any treatment throughout the season limits our possibility to determine the influence of the time point of the onset of combined therapy on eosinophil recruitment to the mucosa. We may, however, suppose that the effectiveness of antihistamine/antileukotriene therapy in inhibiting cellular mucosal inflammation depends on the length of treatment.

Influx of basophils into the nasal mucosa follows allergen provocation and natural exposure in AR patients (30–32). It can be inhibited with both antihistamine pharmacotherapy and allergen specific immunotherapy (32). Also, an antileukotriene zafirlukast has been found to decrease the number of basophils in bronchoalveolar lavage after segmental bronchial allergen provocation (33). In the present study, percentage of basophils in the NLF during the grass pollen season was not increased irrespective of the applied treatment and duration of therapy. The low number of lavage samples and large intersubject variations may explain in part the lack of difference. However, Calhoun et al. (33) observed a similar phenomenon while investigating the effects of zafirlukast on the effects of segmental bronchial allergen challenge. Leukotriene receptor antagonists inhibit basophil migration stronger than that of eosinophils due to different leukotriene-receptor expression on the surface of basophils. Involvement of antileukotrienes in inhibition of progenitor cells differentiation into eosinophils and basophils may also be important. Further studies are needed to elucidate the mechanism of action of antileukotrienes on cellular aspect of inflammation.

Eosinophil cationic protein and tryptase are considered reliable markers of activation of eosinophils and mast cells, respectively. Their levels in nasal secretions and serum are increased after allergen exposure in allergic subjects (9, 27). Eosinophil cationic protein concentration in nasal secretions has been reported as a useful tool in monitoring allergic inflammation (9), and its serum concentration correlates with clinical symptom score (27). Jacobi et al. (22) reported that a 1-week pretreatment with topical or systemic antihistamine (intranasal azelastine or oral cetirizine) reduced the levels of MCT in NLF. Stelmach et al. (34) reported that following a 6-week therapy with antileukotriene (montelukast), there was a significant decrease in serum ECP levels in asthmatic children. To date, the prophylactic activity of antileukotrienes against markers of allergic inflammation remains unclear.

In our study, the levels of ECP in nasal lavages during the pollen season were significantly lower after 12 weeks of combined montelukast and cetirizine treatment. Interestingly, the same treatment applied only during the pollen season had significantly less pronounced effect. This observation further supports our hypothesis that concomitant antihistamine and antileukotriene treatment of AR is more effective when applied during longer period prior to allergen exposure.

We did not observe any difference in NLF MCT levels between patients receiving and not receiving prophylactic montelukast/cetirizine treatment. Jacobi et al. (22) demonstrated prophylactic activity of antihistamine treatment on MCT levels in NLF after allergen provocation. As

MCT is a marker of mast cell activation especially during the early phase of nasal allergic reaction (35), its NLF levels observed in our patients during pollen season may reflect either the chronicity of allergic inflammatory process or the effect of treatment on mast cells activity. Assuming that mast cells activity was inhibited in our patients, we may suppose that prophylactic antihistamine and/or antileukotriene therapy did not have more inhibitory effect than combined antihistamine and antileukotriene therapy started at the beginning of the pollen season.

To our knowledge, this is the first study investigating the possibility of employment of antileukotriene agents into the prophylactic treatment of seasonal AR. A 6-week combined preseasonal treatment with cetirizine and montelukast improved the clinical course of AR during grass pollen season in comparison with treatment started at the beginning of natural exposure to allergen. Clinical improvement was not clearly visible after prophylactic treatment with either drug alone. Data acquired from investigation of selected objective markers of allergic inflammation suggest that prophylactic treatment with concomitant cetirizine and montelukast inhibits migration of eosinophils to the nasal mucosa during natural allergen exposure. Our results point at the need for further studies investigating mechanisms of additive preventive activity of antihistamine and antileukotriene agents.

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