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Prophylactic management of children at risk for recurrent upper respiratory infections: the Preventia I Study

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Summary

Background Given the morbidity and mortality of asthma and the recent dramatic increase in its prevalence, pharmacologic prophylaxis of this disease in children at risk would represent a major medical advance.

Objectives The Preventia I Study was designed to evaluate the efficacy and long-term safety of loratadine in reducing the number of respiratory infections in children at 24 months. A secondary objective was to investigate the benefit of loratadine treatment in preventing the onset of respiratory exacerbations.

Methods Preventia I was a randomized placebo-controlled study involving 22 countries worldwide. The children were 12–30 months of age at enrolment and had experienced at least five episodes of ENT infections, and no more than two episodes of wheezing during the previous 12 months. Phase I was a 12-month double-blind period during which the children were treated with loratadine 5 mg/day (2.5 mg/day for children $\leqslant$ 24 months of age) or placebo. Phase II was a double-blind follow-up period without study medication.

Results Of the 412 children enrolled, 342 and 310 completed Phase I and Phase II, respectively. The results showed a significant decrease in the number of infections in the whole population of children. However, no difference was observed between the loratadine and placebo group. When considering secondary end-points, loratadine was shown to reduce the number of respiratory exacerbations during the treatment phase. None of the 204 children who received loratadine discontinued the study because of drug-related events. Loratadine treatment was not more sedative than placebo and was not associated with cardiovascular events.

Conclusion The strong decrease in the rate of infections in the children at risk of recurrent infections, while not being influenced by loratadine treatment, should encourage future reflection in terms of prophylactic management. This study also confirms the long-term safety of loratadine and its metabolites in young children.

Keywords airway hyper-reactivity, asthma, child, ENT infections, ICAM-1, loratadine, prevention, psychomotor development, rhinovirus, wheezing

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Introduction

Epidemiological studies on a worldwide scale have shown that the incidence of all allergic diseases is increasing, a trend that has been especially obvious over the last two decades [1–4]. Asthma and rhinitis are among the most frequently encountered clinical manifestations of allergy and affect all age groups.

Recent research indicates that events early in life and throughout childhood have an important impact on whether a genetically susceptible person will develop an allergic disease [4, 5]. Among those environmental factors considered important is the type and level of allergen exposure, those allergens in the domestic setting (e.g. dust mite, animal antigens) being most important for asthma and perennial rhinitis. However, allergen exposure alone is judged insufficient to cause organ-specific sensitization and other environmental factors are being sought, including exposure to infectious agents, especially viruses.

The relationship between episodes of infection occurring in early life and the development of respiratory allergy and bronchial hyper-reactivity has been questioned for several

This study was co-ordinated by Alain Grimfeld and Stephen T. Holgate.

See Appendix for participating investigators and centres.

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years. While data suggesting a negative association between viral infections and allergy [6] or asthma [7] are available, several studies support the concept that poor hygiene rather than infections themselves is responsible for preventing atopy [8–11]. This concept is reinforced by findings that the greater number of viral infections in children attending day care in the first 3 years of life was associated with an increased risk of asthma and hayfever [12–14]. Others have found that early infection might instead decrease the risk of developing atopic diseases [15]. However, this effect was only seen in children attending day care at 6 months of age or earlier.

Several clinical and physiological arguments are consistent with a causal link between recurrent upper respiratory tract infections and the onset of airway hyper-reactivity and respiratory allergy in children. From a clinical viewpoint, extensive evidence accumulated both in prospective and retrospective studies indicates that respiratory viral infections in childhood (mainly because of respiratory syncytial virus (RSV)) are associated with a higher prevalence of allergy and asthma at a later stage of life [16–19]. These data are consistent with the hyper-responsiveness of nasal and bronchial mucosa reported in allergic patients experimentally infected with rhinovirus [20, 21]. Pathophysiological arguments include the relationship between viral respiratory infections and the production of IgE against allergens [22], rhinovirus-induced increase in the inflammatory response to antigen inhalation via cytokine production [23, 24], and the pivotal role of intercellular adhesion molecule type 1 (ICAM-1) in both allergen-induced inflammation and viral infections as a receptor of 90% of the rhinoviruses [25, 26].

Taken together, these data suggest that the reduction of the number of infections in children with recurrent upper respiratory infection (URI) may prevent non-specific airway inflammation. To test the hypothesis that a long-term antihistamine-based treatment could reduce the number of infections (and their impact on airway hyper-reactivity) in children at risk, a large-scale multinational study involving 400 children throughout the world was started in 1996. The aim of the Preventia Study was to evaluate the action of loratadine syrup, a 2nd-generation antihistamine, on the number of respiratory infections in young children at risk. The primary objective also included the assessment of the long-term safety of loratadine in young children in terms of adverse events, including somnolence and vital signs. A secondary objective was to investigate the benefit of loratadine treatment in preventing the onset of respiratory exacerbations and reducing the number of wheezing episodes. Loratadine was chosen as the test drug because of its pharmacological properties [27–31] and its safety reported in children of school age treated for seasonal rhinitis during few weeks [32]. In addition to inhibiting the release of various mediators, including histamine [27, 28], loratadine down-regulates the expression of ICAM-1 on the surface of epithelial cells [29–31]. Besides, loratadine is not associated with a sedative effect [32] or a risk of cardiovascular events [33]. The Preventia Study provides unique and important data for the prophylactic management of respiratory disease in young children at risk as well as for the long-term safety of loratadine in children less than 2 years old.

Patients and methods

Patient enrolment

To be included in the study, children had to be between 12 and 30 months of age at enrolment and have had no more than two episodes of wheezing. They had to have experienced at least five episodes of rhinitis, rhinopharyngitis, acute otitis media, laryngitis or bronchitis during the previous 12 months. Children had to be in good general health, free of any clinically significant disease other than atopy or respiratory infections that could interfere with the study. A child's parent/guardian had to be willing and able to comply with the requirements of the study, and to give written informed consent prior to enrolment.

Exclusion criteria were as follows: child suffering from any chronic pulmonary disease, allergy to loratadine syrup or any other drug, medical illness (renal, hepatic, cardiovascular and neurologic), abnormal vital sign, abnormal weight or height not because of a known underlying disease or clinically significant malnutrition, clinically significant abnormal laboratory values (except if because of a known underlying disease), personal or familial (parent or sibling) history of sleep apnoea, participation in a drug trial within 30 days prior to study entrance, desensitization or immunotherapy with allergen extracts undergone prior to enrolment, immunosuppressive treatment or radiation therapy over the past 6 months (or expected to be required during the study). Previous drug administration required a washout period prior to enrolment, depending on the drug: systemic corticosteroids (30 days), inhaled or nasal corticosteroids (14 days), cromolyn sodium (14 days), antihistamines (7 days) and immunostimulators (30 days).

A total of 413 children were enrolled at 51 centres in Europe, South Africa, Asia, Central and South America (see Table 1). The first child was enrolled in September 1996, and the last patient completed the study in December 2000. The protocol of the study complied with Principles of Good Clinical Practice and was approved by local ethical committees in conformity with the laws, regulations, and guidelines applicable in each country where children were enrolled. At the time of inclusion, a written informed consent was completed by the parents.

Study design

The study consisted of two phases. Phase I (treatment phase) was a 12-month double-blind, randomized period during which the children received loratadine or placebo. Phase II was a 12-month follow-up without study medication. During the treatment phase, children between 12 and 24 months of age were administered loratadine syrup (Claritin® syrup, Schering-Plough, Kenilworth, NJ, USA) at a single daily dose of 2.5 mL (loratadine 2.5 mg). Children over the age of 24 months were administered a single daily dose of 5 mL (loratadine 5 mg). A total of 412 children were randomized to loratadine group ($n = 204$) or placebo group ($n = 208$). Randomization was applied to each of the 51 centres, in which a similar number of children in loratadine and placebo groups was monitored. The children enrolled were seen after 1 month, and every 3 months thereafter during both the treatment and follow-up phases. The primary objective of the

Table 1. Enrolment of children at the various centres

Country	Children (*n*)	
	Loratadine	Placebo
Europe		
Austria		1
Belgium	1	1
Czech Republic	22	22
Denmark	2	1
France	40	43
Greece	13	13
Hungary	24	25
Italy	16	15
the Netherlands	1	2
Norway	4	3
Poland	4	4
Portugal	1	1
Spain	6	6
Switzerland	1	1
UK	6	6
Asia		
China	2	3
Singapore	7	6
Thailand	4	4
Central/South America		
Ecuador	20	20
Mexico	12	12
Venezuela	10	11
Africa		
South Africa	8	8
Total	204	208

study was to demonstrate the efficacy of loratadine syrup in reducing the number of infections, as well as the long-term safety of the drug. Secondary objectives included onset and number of respiratory exacerbations, and the number of physician contacts and hospitalizations.

Efficacy parameters

The primary efficacy variable was the total number of respiratory infections (per patient and per phase), which was recorded at each visit during both phases (treatment and follow-up). Respiratory infections mentioned at the time of the enrolment or reported by the parent/guardian at each visit had been clinically confirmed by a physician (the investigator or the physician who had made the child enter the study) prior to the visit. The term 'wheezers' refers to children who experienced wheezing episodes clinically confirmed by a physician. The secondary efficacy variables were: the number of children with an onset of respiratory exacerbations, the total number of respiratory exacerbations, the number of physician contacts (visits or phone calls other than study scheduled) because of respiratory infections or respiratory exacerbations, the number of days of hospitalization because of respiratory infections or exacerbations. Respiratory exacerbations were defined as three consecutive nights with one or more episodes of nocturnal cough with sleep disturbance and/or three separate incidents of wheezing diagnosed as such by a medical professional. The investigators were asked to pay maximum attention to instructing the parent/guardian at the first visit. All the variables were recorded at each visit.

Safety parameters

The safety parameters included: adverse events reporting, discontinuation from the study because of adverse events, physical examination, laboratory values, electrocardiogram (EKG) and psychomotor development (including the following variables: the child starts to: (1) pull up to stand; (2) walk with support; (3) stand alone; (4) say some words; (5) climb stairs with assistance; (6) run; (7) say short sentences; (8) balance on one foot; (9) catch and throw large ball; (10) pour milk from pitcher into cup without spilling; (11) sort objects by colour and size; (12) count to 10; (13) put on and take off shoes; (14) use words to share toys, take turns; (15) turn pages of a book; (16) make tower of more than six cubes; (17) help out with chores such as setting the table, watering plants and wiping up spills). Vital signs and psychomotor development were evaluated at each visit. Changes in physical examination were evaluated at visits 1, 6 (end of treatment phase) and 10 (end of follow-up phase). Laboratory values and EKG were recorded at visit 1 and at the end of the 12-month treatment phase.

Statistical analysis

Descriptive statistics were to be provided along with a *t*-test to compare the continuous variables and Cochran–Mantel–Haenszel test for discrete variables. The number of respiratory infections during the treatment phase, during the follow-up period, and during the entire study were compared between loratadine and placebo groups using a linear model based on ranks with treatment and centre as factors and significant (at 0.25 level) baseline variables as covariates. The interaction effect was considered significant at 0.20 level to determine removing centre effects from the models.

The number of patients with onset of respiratory exacerbations and the total number of exacerbation episodes were compared across the two groups using Fisher's exact test and the Wilcoxon Rank Sum test, respectively.

The primary analysis population was decided to be the intend-to-treat (ITT) population that includes all randomized children who received at least one dose of the study medication. Analyses were performed using the evaluable population as well, primarily for consistency checks. All statistical interferences were performed at a 0.05 level of significance unless otherwise specified.

The safety parameters during the treatment phase were compared across the two groups using Fisher's exact test.

Results

Patient characteristics

The two groups of randomized children were comparable in terms of demographics at baseline (Table 2). Of the 412 children randomized to the loratadine or the placebo group, approximately 75% completed both the treatment and follow-up phases of the study. Discontinuation was mainly because of failure to follow up or parental decision. Only one

Table 2. Demographics and patient distribution

	Loratadine* ($n = 204$)	Placebo* ($n = 208$)
Mean age (months)	23.9 ± 5.2	24.0 ± 5.7
Age groups (%)		
12 to <18 months	17.7%	19.2%
18 to <24 months	15.7%	13.9%
24 to <30 months	62.7%	56.7%
30 months	3.9%	10.1%
Sex (male/female)	131/73	119/88†
Race (White/Black/ Hispanic/Asian/other)	149/3/38/13/1	152/3/37/14/1†
Number of respiratory infections in previous year	8.5 ± 3.3	8.1 ± 2.8
Presence of allergies	27.1%	26.4%
Day-care attendance		
At baseline	35.8%	33.3%
At the end of treatment phase	35.5%	42.0%
Passive smoking		
Smoker in house	39.2%	37.6%
Mother smoking during pregnancy	11.8%	10.2%
Treatment phase completed	164	177
Treatment and follow-up phases completed	147	163
Follow-up phase discontinuation	13	9

*No statistical difference between the groups whatever the item considered.
†Total = 207.

patient had to discontinue from the study because of an adverse event in the placebo group. The other reasons for discontinuation included administrative problems, decisions of the parents/guardians not to continue, the fact that patients did not meet protocol eligibility or failure to follow up.

Number of infections

The total number of infections was the primary parameter to be investigated. No statistical difference was noted between the two groups in the average number of infections per patient during each phase of the study and during the whole 24-month study period (Table 3). However, a decrease in the mean number of infections was observed in both groups during the first months of the study (Fig. 1), which became highly significant 4 months after the enrolment ($P<0.001$ compared with baseline). A similar decrease was still observed when different age groups (from less than 18 months to more than 30 months) or geographical areas were considered (data not shown). The analysis of the subgroup of allergic children was performed (Table 3). At the end of the whole study period, the average numbers of infections in allergic children were 3.7 and 4.8 in the loratadine and placebo groups, respectively. However, the difference observed from this subgroup analysis, including only one-fourth of the whole population of children, was not found to be statistically significant.

Table 3. Total number of respiratory infections per patient in the whole and allergic populations of children (ITT population)

	Number of infections per patient *(n)*		
	Loratadine	Placebo	*P*-value*
12-month treatment phase			
All children	6.2 (204)	6.2 (208)	0.60
Allergic children	6.0 (53)	6.3 (53)	0.79
24-month study period			
All children	11.6 (156)	11.3 (171)	0.67
Allergic children	3.7 (36)	4.8 (39)	0.20

*Wilcoxon's rank-sum test.
ITT, intend-to-treat.

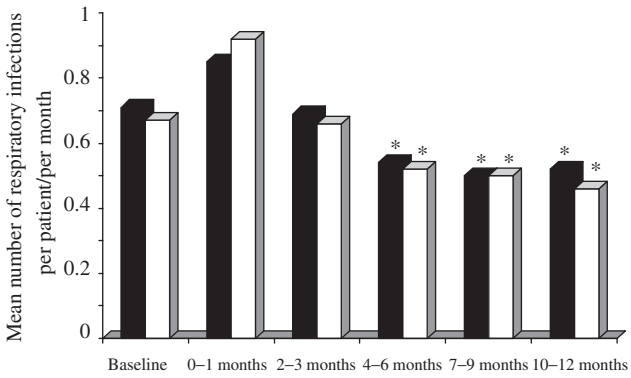

Fig. 1. Mean number of respiratory infections per patient/per month during the treatment phase (intend-to-treat population). The children enrolled were randomized to Loratadine syrup (■) or placebo (□) group. For each child, the number of infections per month was recorded at baseline, after 1 month and every 3 months. The mean numbers of infections per patient and per month during the treatment phase are shown. *$P<0.001$ compared with baseline. No statistical difference between groups.

Table 4. Mean number of respiratory exacerbations per patient during the 12-month treatment phase

	Loratadine (*n*)	Placebo (*n*)	*P*-value
ITT population	0.8 (199)	1.1 (203)	0.02*
Evaluable patients	0.8 (158)	1.2 (168)	<0.01*

*Wilcoxon's rank-sum test.
ITT, intend-to-treat.

Respiratory exacerbations

The effect of loratadine on the onset of respiratory exacerbations and the number of episodes (including wheezing and/or cough) was also evaluated. The average number of episodes per patient in the ITT population during the 12-month treatment phase was 0.8 and 1.1 in the loratadine and the placebo group, respectively ($P = 0.02$). Corresponding values in the evaluable population were 0.8 and 1.2 ($P = 0.001$) (Table 4). When the whole 24-month study period including the 12-month phase without treatment was considered, the difference between groups was no longer observed (Table 5). However, a statistically significant effect of loratadine was still observed on the number of respiratory exacerbations in Phase II for patients who had experienced wheezing during the treatment phase (Phase I), the average

Table 5. Onset and number of respiratory exacerbations in phases 1 and 2

	Loratadine ($n = 156$)	Placebo ($n = 171$)	*P*-value
Exacerbation present (% patients)	50	45	0.3775*
Mean number of episodes per patient	1.8	1.9	0.5984†
Number of episodes in 'wheezers'	3.7	4.3	0.0497‡

*Fisher's exact test.
†Wilcoxon's rank-sum test.
‡Generalized linear model with Poisson distribution.

Table 6. Most frequent adverse events in phases 1 and 2

	Loratadine ($n = 165$) *N* (%)	Placebo ($n = 177$) *N* (%)	*P*-value*
Pharyngitis	31 (18.8)	32 (18.1)	0.976
Bronchitis	26 (15.8)	23 (13.0)	0.564
Otitis media	15 (9.1)	23 (13.0)	0.328
Gastroenteritis	17 (7.9)	14 (7.9)	0.560
Rhinitis	13 (7.9)	13 (7.3)	0.999
Fever	11 (6.7)	13 (7.3)	0.974
Varicella	14 (8.5)	8 (4.5)	0.202
Coughing	12 (7.3)	9 (5.1)	0.536
Tonsillitis	9 (5.5)	9 (5.1)	0.999
Viral infection	9 (5.5)	8 (4.5)	0.880
Vomiting	9 (5.5)	6 (3.4)	0.504

*Fisher's exact test.

number of respiratory exacerbations being 3.7 and 4.3 in the loratadine and the placebo group, respectively ($P = 0.0497$).

As secondary variables to be evaluated, physician contacts and hospitalization because of respiratory infections were comparable in the two groups. Mean rates of physician contacts during the whole 24-month period of the study were 0.546 and 0.505 in the loratadine and the placebo group, respectively. The average monthly hospitalizations per patient did not reach 1 day throughout the study, and were comparable in the two groups.

Safety results

The most frequent adverse events reported during the treatment phase are presented in Table 6. Almost all reported adverse events were mild. The only serious event resulting in discontinuation from the study was in the placebo group. There were no statistical differences between loratadine- and placebo-treated children in any other safety parameters such as physical examination, psychomotor development, and in any safety parameters in patients below the age of 24 months at the time of enrolment. The safety profiles of loratadine and placebo groups were quite comparable, and no major clinical problem occurred that could have been attributed to the study medication.

There was no appreciable difference between the two groups in safety parameters during the treatment phase, including vital signs, and EKG (Table 7). Regarding EKG, changes from baseline were noted in four patients from each group. Findings were disturbances in ventricular repolarization ($n = 1$), lengthening of QT interval ($n = 1$), sinus bradycardia ($n = 1$) and sinus arrythmia ($n = 1$) in the loratadine group, and lengthening of PR interval ($n = 1$), right ventricular hypertrophy ($n = 1$), lengthening of QT interval ($n = 1$) and left overload ($n = 1$) in the placebo group. There was no difference between groups regarding laboratory parameters (data not shown). The other safety parameters evaluated (insomnia, irritability, somnolence) were reported at low rates in both the placebo and the loratadine groups. Of special interest was the rate of somnolence during the 12-month treatment phase, which was reported in only one patient in the loratadine group (0.5%) and two patients in the placebo group (1%).

Table 7. Safety parameters during the 24-month treatment phase

	Loratadine	Placebo
	$n = 204$	$n = 208$
Vital signs (12 months – baseline)		
Temperature (°C)	-0.1 ± 0.47	0.0 ± 0.55*
Pulse (b.p.m.)	-5.3 ± 16.33	-5.9 ± 16.33*
Respiratory rate (per min)	-3.0 ± 9.68	-1.3 ± 10.95*
Systolic blood pressure (mmHg)	-0.8 ± 13.81	-0.4 ± 14.47*
Diastolic blood pressure (mmHg)	-0.5 ± 10.79	0.5 ± 12.38*
	$n = 143$	$n = 155$
EKG (new/changed findings)	2.8%	2.6%*
	$n = 199$	$n = 198$
Other disorders		
Insomnia	0.0	1.0*
Irritability	0.0	0.5*
Somnolence	0.5	1.0*

EKG, electrocardiogram.
*No statistically significant difference between the two groups.

Discussion

Extensive evidence accumulated both in prospective and retrospective studies indicating that lower respiratory viral infections in childhood (mainly because of RSV) are associated with a higher prevalence of allergy and asthma at a later stage of life [16–19]. These data have been reinforced by recent epidemiological studies showing a direct link between respiratory infections and asthma and/or respiratory allergy in young children attending day care [12–14]. These data are balanced by the inverse relationship observed in children attending day care before the age of 6 months [15], the relevance of which may be minimized at least in western European countries where most parents usually prefer to place their children in day care later.

The aim of the Preventia Study was to test whether or not treating allergy with an antihistamine could represent a preventive measure to reduce infections and exacerbation of related symptoms in allergic subjects. Three main arguments in favour of such a hypothesis emerged: (i) the strong assumption of a causal link between recurrent upper respiratory tract infections and the onset of airway hyperreactivity and respiratory allergy in children; (ii) the pivotal role of ICAM-1 in both allergen-induced inflammation, via the attraction of inflammatory cells, and viral infections as a virus receptor (in 90% of rhinovirus); and (iii) the fact that

early treatment of atopic and non-atopic children with recurrent URIs may reduce the number of these infections and consequently prevent non-specific airway hyper-reactivity and the development of allergy.

More than 400 children at risk of recurrent ENT and respiratory infections were enrolled throughout the world, 75% of whom completed both the 12-month treatment phase and the 12-month follow-up period without medication. Loratadine syrup was chosen as the test drug, and this study is the largest one on long-term evaluation (including efficacy and safety) of an antihistamine in children less than 2 years old.

The primary objective of the study was the rate of clinically confirmed respiratory infections supposed to be reduced in the loratadine group. This hypothesis was not verified as there was no significant difference between the two groups. However, a progressive decrease in the number of infections per month was observed, which became significant after 4–6 months and was maintained similarly after 9 and 12 months of treatment. The reduction in the rate of infections was the same in the two groups without distinction between placebo- and loratadine-treated children. One can postulate that this decrease might be partly as a result of a bias related to parental recall of infections during the 3 previous months. However, the reporting of infection by the parent/guardian was based on a clinical observation made by a physician, which makes this hypothesis unlikely. Two explanations could therefore be provided. The first one would consider the effect of the maturing immune system in children of such low age. While no difference was seen when comparing the youngest and the oldest children enrolled in the study (less than 18 and more than 30 months of age, respectively), such a hypothesis cannot be ruled out as the ages of children were similar and immune development continues throughout the infancy. The second explanation concerns the benefit derived from excellent medical attention and careful observation by both physicians and parents. The possibility that a form of immune protection produced such a 'placebo effect' cannot be excluded, as it is clear that virus infections are strongly influenced by stress. The reassurance drawn from frequent physician contacts might help alleviate some of the natural stress of bringing up a child through the early years. Subgroup analysis, which was not planned for at study onset could have been helpful in answering this question, especially for countries/cities where the impact of close attention/careful information would have been more significant.

Although no difference was observed between the two groups of children, a positive action of loratadine that would have been masked by the dramatic follow-up effect cannot be excluded. This hypothesis is supported by the significant action of loratadine on the number of respiratory exacerbations during the treatment phase. The interpretation of the results is made complicated and limited because of the low number of exacerbations by patient during the study. Furthermore, respiratory exacerbations determined by the parent/guardian and/or the physician included cough and wheezing episodes, without distinction, so that it is not possible to determine whether loratadine affected illnesses with cough, illnesses with wheeze or both. What might be interesting is the speculation of what long-term loratadine would have done to children experiencing more frequent or severe episodes of wheezing. However, the study had not been designed to answer this question.

The low but significant decrease in the number of respiratory exacerbations in children treated with loratadine was most likely as a result of a down-regulatory effect on ICAM-1 expression [27–31]. In this respect, one could have expected loratadine to prevent respiratory infections in the subpopulation of allergic patients, as it is known that loratadine-driven ICAM-1 down-regulation happens under the conditions of allergen or rhinovirus-induced ICAM-1 expression. The subgroup analysis focused on allergic children did not show any statistically significant group-specific difference in favour of loratadine. These data must be cautiously interpreted as the statistical power of this analysis, not planned at the time of the study design, was limited by the low percentage of allergic patients in the whole population of children. Further studies including larger cohorts of allergic children would be required to show whether or not an antihistamine-based treatment may prevent URIs and subsequent airway inflammation.

The Preventia Study was also a good opportunity for testing the safety of loratadine in young children treated each day for 1 year. None of the 204 children who received loratadine discontinued the study because of drug-related events. Indeed, the loratadine group was statistically comparable with the placebo group regarding all the safety parameters evaluated, including serious adverse events or vital signs. Concerning, specifically somnolence, a well-known putative effect of some antihistamines, the results confirm the previous short-term study showing that loratadine was not more sedating than placebo, as previously shown in children suffering from allergic rhinitis [32]. Finally, these long-term safety data also confirm that loratadine and its metabolites, when administered at the usual dose, are not associated with an increased risk of cardiovascular events.

In conclusion, the study failed to demonstrate a prophylactic effect of loratadine on the number of respiratory infections in the whole population of young children enrolled, while a low but significant action on respiratory exacerbations was observed. The apparent lack of correlation between the action of loratadine and the prevention of URIs must be modulated by the strong decrease in the rate of infections in both groups, which could have masked a putative effect of the drug in allergic children. The results of Preventia, associated with the long-term safety of loratadine, should encourage future reflection and further studies on the management of young children at risk of recurrent infections.

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Appendix

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