

A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up

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Background: Because asthma is not a curable condition, the development of strategies for prevention of the disease has a high priority. Atopic dermatitis is a common precursor to the development of asthma, and 2 studies have suggested that the use of an H₁ receptor antagonist might reduce the development of asthma while the treatment is being administered, at least in subgroups with evidence of high IgE levels. However, no trial to date has conducted follow-up after the initial treatment has been stopped to establish whether the intervention has merely suppressed symptoms or truly prevented disease. **Objective:** We sought to establish whether the use of cetirizine compared with placebo for 18 months in infants with atopic dermatitis suppressed or truly delayed the onset of asthma, even after cessation of therapy.

Methods: The Early Treatment of the Atopic Child study was a double-blinded, parallel-group, randomized trial of 0.25 mg/kg body weight cetirizine administered twice daily compared with placebo given to infants between 1 and 2 years of age with atopic dermatitis. After 18 months of treatment, follow-up continued for a further 18 months. This article reports the outcome over the full 3 years of follow-up and relates the outcomes to the allergic status on the basis of IgE antibody measurements at recruitment.

Results: Although there was no difference in cumulative prevalence of asthma between active and placebo treatment in the intention-to-treat population ($P = .7$), those infants with evidence of sensitivity to house dust mite, grass pollen, or both who were treated with cetirizine were significantly less likely to have asthma compared with those treated with placebo over the 18 months of treatment ($P = .005$ and $.002$, respectively), and this effect was sustained for the grass pollen-sensitized infants over the full 36 months ($P = .008$). In the house dust mite-sensitized group there was a gradual narrowing of the difference between active and placebo treatment in terms of cumulative prevalence of asthma at the end of 36 months but

no evidence of a rebound immediately after the treatment stopped ($P = .04$). In the placebo population there was a significantly higher risk of development of asthma in those sensitized at baseline to egg (relative risk, 1.4 [95% CI, 1.1-1.7]), house dust mite (relative risk, 1.6 [95% CI, 1.3-1.9]), grass pollen (relative risk, 1.7 [95% CI, 1.4-2.1]), or cat (relative risk, 1.5 [95% CI, 1.2-1.9]). Early and persistent sensitization conferred a higher risk than transient or later sensitization. **Conclusions:** Cetirizine compared with placebo truly delays or, in some cases, prevents the development of asthma in a subgroup of infants with atopic dermatitis sensitized to grass pollen and, to a lesser extent, house dust mite. Further studies are required focusing specifically on sensitized groups to substantiate this finding. The study also highlights risk factors for asthma in infants with atopic dermatitis and indicates that early and persistent aeroallergen sensitization confers a higher risk than later development of sensitivity. (*J Allergy Clin Immunol* 2001;108:929-37.)

Key words: Atopic dermatitis, asthma, prevention, house dust mite, grass pollen, cetirizine, antihistamine, children

Highly effective pharmacotherapy is available to control asthma, but to date, no cure has been identified. The natural history of the disease appears to evolve independent of treatment. Thus children with infrequent episodic wheezing do not have any evidence of abnormal lung function compared with nonwheezing control subjects, even after 28 years' follow-up and irrespective of whether inhaled corticosteroids have been used.¹ Conversely, the degree of lung function abnormality and bronchial hyperresponsiveness at presentation with asthma are the main factors associated with ongoing disease, abnormal lung function, and persistent hyperresponsiveness in early adulthood, again irrespective of therapy.²

The current paradigm that dictates the therapeutic approach to asthma is that airway inflammation involving particularly eosinophils and mast cells is present even during relatively asymptomatic periods.³ Because the degree of eosinophilic infiltration and the thickness of the lamina reticularis as a component of remodeling do not correlate with disease duration, even in young children, it is possible that the pathologic changes were present before the first symptoms of asthma were manifested in early life.⁴ Under such circumstances, it seems unlikely that current conventional therapeutic approaches, even if introduced very early after the onset of symptoms, will modify the outcome. Thus we must focus attention on

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Supported by UCB Pharma, Brussels, Belgium.

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Received for publication May 17, 2001; revised September 4, 2001; accepted for publication September 7, 2001.

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0091-6749/2001 \$35.00 + 0 1/81/120015

doi:10.1067/mai.2001.120015

Abbreviation used

ITT: Intention to treat

presymptomatic intervention before the immunopathology of the disease is fully established.

Repeated studies have shown that atopic dermatitis is a common precursor to the development of asthma.^{5,6} Therefore this dermatologic problem is a good target for introducing presymptomatic preventive strategies. The Early Treatment of the Atopic Child study has been a multicountry, multicenter, double-blinded, randomized, placebo-controlled trial of the use of cetirizine in preventing the onset of asthma in children with a family history of atopy who have atopic dermatitis. The results of 18 months of treatment have already been reported.⁷ These showed that although there was no difference between active and placebo therapy in the intention-to-treat (ITT) population, subgroup analysis of those with evidence of sensitivity to either house dust mite or grass pollen at recruitment between 1 and 2 years of age had a lower incidence of asthma over the 18-month treatment period with cetirizine compared with placebo, and this was a highly relevant clinical effect.

One other trial has investigated the hypothesis that asthma may be prevented by pharmacotherapy in children with atopic dermatitis using ketotifen. This latter trial showed, in 121 infants with atopic dermatitis, that ketotifen compared with placebo over a 1-year period resulted in significantly less asthma. However, this effect was only seen in those children who had evidence of raised total IgE levels at recruitment and not in those with normal total IgE levels.⁸ Cetirizine was chosen for our study not only for its antihistaminic effect but also because it has been shown to inhibit allergen-induced eosinophil trafficking into the skin, nose, lungs, and conjunctiva.⁹ As such, it has the potential of inhibiting the development of eosinophilic inflammation in infants sensitized to aeroallergens and with a high risk of asthma development. It might therefore be expected to have a carryover effect beyond the period of initial treatment.

No trial has ever conducted any follow-up after the initial treatment has been stopped to establish whether the intervention has merely suppressed symptoms or truly delayed or prevented the disease. Thus in the Early Treatment of the Atopic Child study, an 18-month posttreatment follow-up has been conducted, and this forms the basis of the current report.

METHODS

The study design is outlined in detail in our previous report.⁷ In brief, children between 1 and 2 years of age with active symptoms of atopic dermatitis for at least 1 month were considered suitable for enrollment. All the infants had at least one parent or sibling with a history of atopic dermatitis, allergic rhinitis, asthma, or some combination thereof. The diagnosis of atopic dermatitis was based on standard criteria involving a typical eczematous or lichenified dermatitis affecting the face, skin flexures, or both with evidence of

pruritis. Children were excluded if they had had any episodes of wheezing beyond the age of 6 months or more than 1 episode of persistent nocturnal coughing, as well as any other condition likely to obscure the diagnosis of asthma. Other exclusion criteria included any other chronic pulmonary disease or other severe disorder likely to interfere with the study drug or observation of outcome. Subjects were also excluded if they were taking regular antihistamine, oral cromoglycate, or systemic steroids in the previous few weeks before recruitment. Ceasing these medications allowed investigators to establish whether their use had any effect on the atopic dermatitis or whether these treatments were in some way suppressing the manifestations of asthma. During the course of the study, choice of treatment for any conditions manifested by the children was left to the clinical investigators or other physicians managing the children. It was suggested that other antihistamines should be used with caution, and recommendations were made on the stepwise management of asthma if it developed.

Cetirizine or identical placebo oral solution was administered at a dose of 0.25 mg/kg twice daily (total daily dose of 0.5 mg/kg) as an oral solution of 10 mg/mL. The outcome of the 18-month treatment period has been reported elsewhere.⁷ At the end of this period, a further 6-month posttreatment follow-up after discontinuation of medication sustained the blinding regarding the study medication. The further 12-month follow-up proceeded on an open-label basis as far as the investigators were concerned. Only a tiny minority of parents were aware of the nature of the treatment their child had received.

Clinic visits occurred at screening and then immediately before commencement of therapy, with subsequent visits being at 1 month, 3 months, and every 3 months thereafter during the 18-month treatment period. Posttreatment follow-up was at 6, 12, and 18 months after treatment had ceased. Blood samples were collected at baseline and at 3, 12, 18, 24, and 36 months after commencing the study. The measurement of total IgE, IgE antibodies to egg, milk, house dust mite, grass pollen, and cat, as well as hematology and blood-chemistry parameters, were performed. Six-lead electrocardiography (DI, DII, DIII, AVL, AVF, and AVR) was performed at baseline and at 1, 18, and 24 months after commencing the study for measurement of the QT and RR intervals. Subsets of children also had behavior and developmental assessments during the course of study, and these will be reported elsewhere.

At each assessment visit, the atopic dermatitis was assessed for severity by using the SCORAD scale.¹⁰ The parents' day-by-day recording of respiratory symptoms was reviewed by the clinical investigator, routine clinical history was obtained, and examinations were performed, with all data being recorded on standard clinical record forms.

The primary end point for efficacy was the time to the onset of asthma, which was defined as 3 episodes separated by at least 7 days, either of nocturnal cough with sleep disturbance lasting for at least 3 consecutive nights, 3 episodes of wheezing, or a combination of the 2 symptoms. The data for all patients were reviewed by a data-review committee on the basis of the above criteria, following a procedure with a careful protocol agreed on before the start of the review. The diagnosis of asthma, the date of the first attack, and the number and duration of any subsequent episodes were recorded, as was the use of any medications.

Sample size was based on the primary end point after the 18-month treatment period. It was based on an expected incidence of asthma of 40% in the placebo group after 18 months' treatment. A decrease of 30% in incidence (28% in the cetirizine group compared with 40% in the placebo group) was considered to be clinically worthwhile. Five hundred infants needed to complete the 18-month study to have 80% power to demonstrate such a difference given that the statistical tests were to be carried out 2-tailed at the 5% level

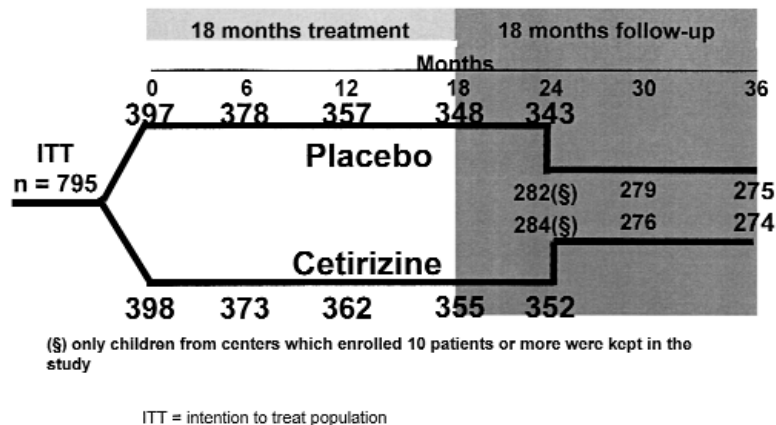


FIG 1. Attrition diagram for the 36-month study period. The ITT population refers to those who attended the clinic where the first prescription for the study medication was issued. All centers enrolling patients continued observations until 24 months' follow-up. Thereafter, only those centers at which 10 patients or more were enrolled were kept in the study, which accounts for the smaller numbers followed to 36 months.

of significance, and taking into account potential dropout, at least 700 should have been recruited. All children maintained in the study entered the 6-month blinded follow-up period. However, for the further 12-month posttreatment follow-up period, only those children from centers having randomized 10 or more patients continued.

The evaluation of efficacy was primarily based on the time to onset of asthma. Descriptive statistics included the frequencies of patients with asthma in the 2 treatment groups, the cumulative incidence curves of occurrence of asthma (estimated with the Kaplan-Meier approach), and the median time to onset of asthma with its 95% CI. The comparison of the 2 treatment groups was performed with the log-rank test.

An analysis was performed of onset of asthma, considering the patients in the placebo group. The purpose of the analysis was to determine whether the presence or absence of IgE sensitization at baseline was a prognostic factor for occurrence and time to onset of asthma. This analysis included the calculation of the frequency distribution of the occurrence of asthma in patients sensitized or not sensitized and the relative risk (with 95% CI) for development of asthma when sensitized. All allergens tested by means of IgE antibody assay were considered.

The observation that sensitization to certain allergens was associated with a statistically significantly higher risk of development of asthma called for a more in-depth analysis of any treatment interactions with such baseline characteristics. In the first instance, such interactions were evaluated for each of the allergens separately by means of the Breslow-Day test. These analyses revealed statistically significant interactions between treatment and some of the specific IgEs. Therefore a multivariate analysis (Cox proportional hazards) was performed to model the time to onset of asthma on the basis of treatment and the status of each of the 5 specific IgEs at baseline. This analysis was performed in a stepwise way, considering 2-way and 3-way interactions between factors. The occurrence and time to onset of asthma was described in the subgroups of patients sensitized and not sensitized to study these interactions thoroughly.

An additional analysis was based on the occurrence of active asthma, defined as patients who became asthmatic during the study and wheezed at least 1 day in the last 12 months of follow-up. The relationship between the occurrence of active asthma and the development of sensitization to egg, grass pollen, and house dust mite was analyzed in the placebo group.

Descriptive statistics were given for the percentage of days of use of each of the asthma and atopic dermatitis medications. The comparison of the treatment groups was based on the Mann-Whitney test.

Ethics committees approved the study in the institutions of every investigator who participated in the study.

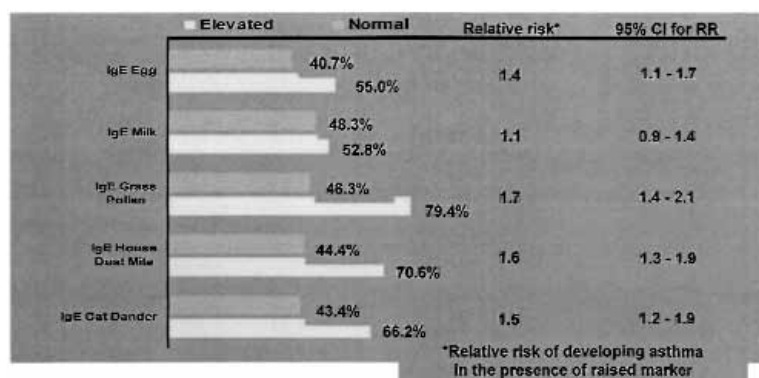
RESULTS

The attrition diagram for the whole investigation period is presented in Fig 1. Data on 830 screened infants were available, and 795 constitute the ITT population. Dropouts were very much lower than expected at all stages of the study, such that over 500 children were still in the study after 3 years. Dropout rates were evenly distributed between active and placebo therapy during the 18-month posttreatment follow-up, and none were the result of adverse events. Reasons were varied and equally distributed between the 2 treatment arms.

Demographic and other baseline characteristics of the ITT population were very similar in both treatment groups in relation to age, sex, biologic markers, SCORAD rating, and family history of allergy, except for sensitization to egg, which was more frequent in the placebo group. Furthermore, no biases were detected with regard to these variables between the children who stopped the study after 6 months of posttreatment follow-up and those who entered the further 12-month posttreatment follow-up period. Patient baseline characteristics for the latter are shown in Table I.

Fig 2 gives details of the occurrence of asthma in the placebo group broken down by the presence or absence of IgE sensitization to the 5 allergens at recruitment. It can be seen that evidence of sensitization to grass pollen, house dust mite, and cat were highly significantly associated with an increased risk of development of asthma over the 3-year follow-up period, which is very similar to the figures already identified after 18 months. However, although egg sensitivity at recruitment was not associated with an increased risk of asthma after 18 months, this association was significant after 3 years. No significant effect associated with milk sensitization was shown.

Overall, in the ITT population there was no statistically significant difference between the number of children



Raised IgE allergen specific antibody ≥ 0.35 kU/L
Normal = less than 0.35 kU/L

FIG 2. The percentages of children in the placebo limb of the study in whom asthma developed during the 36-month follow-up period identified by the presence or absence of specific IgE antibodies to 5 allergens, as indicated by an antibody level of 0.35 kU/L or greater. Relative risks and 95% CIs for the development of asthma are indicated for each allergen. *RR*, Relative risk.

TABLE I. Baseline characteristics of patients who entered the further 12-month posttreatment follow-up period

Baseline characteristics	Placebo (n = 282)	Cetirizine (n = 284)	Total (n = 566)
Age (mo) at inclusion			
n	282	284	566
Mean $\pm$ SD	17.1 $\pm$ 4.1	16.9 $\pm$ 4.2	17.0 $\pm$ 4.2
Median	16.3	16.2	16.2
Minimum-maximum	10-25	11-28	10-28
Sex			
Male	167 (59.2%)	175 (61.6%)	342 (60.4%)
Female	115 (40.8%)	109 (38.4%)	224 (39.6%)
SCORAD score at baseline			
n	282	283	565
Mean $\pm$ SD	24.9 $\pm$ 14.0	24.1 $\pm$ 13.8	24.5 $\pm$ 13.9
Median	23.1	22.0	22.3
Minimum-maximum	0-80	0-74	0-80
Asthmatic father	62 (22.0%)	61 (21.5%)	123 (21.7%)
Asthmatic mother	58 (20.6%)	46 (16.2%)	104 (18.4%)
Asthmatic father or mother	113 (40.1%)	104 (36.6%)	217 (38.3%)
Father with AD	56 (19.9%)	62 (21.8%)	118 (20.9%)
Mother with AD	87 (30.9%)	82 (28.9%)	169 (29.9%)
Father or mother with AD	131 (46.5%)	132 (46.5%)	263 (46.5%)
Total IgE (PRIST)			
Normal (<0.30 kUA/L)	131 (51.2%)	133 (53.0%)	264 (52.1%)
Elevated	125 (48.8%)	118 (47.0%)	243 (47.9%)
IgE grass pollen (GX1)			
Normal (<0.35 kUA/L)	210 (91.3%)	206 (89.2%)	416 (90.2%)
Elevated	20 (8.7%)	25 (10.8%)	45 (9.8%)
IgE HDM (D1)			
Normal (<0.35 kUA/L)	198 (81.5%)	204 (83.3%)	402 (82.4%)
Elevated	45 (18.5%)	41 (16.7%)	86 (17.6%)
IgE cat dander (E1)			
Normal (<0.35 kUA/L)	174 (78.0%)	174 (79.5%)	348 (78.7%)
Elevated	49 (22.0%)	45 (20.6%)	94 (21.3%)
IgE egg (F1)			
Normal (<0.35 kUA/L)	100 (48.3%)	124 (60.2%)	224 (54.2%)
Elevated	107 (51.7%)	82 (39.8%)	189 (45.8%)
IgE milk (F2)			
Normal (<0.35 kUA/L)	162 (64.3%)	169 (68.2%)	331 (66.2%)
Elevated	90 (35.7%)	79 (31.9%)	169 (33.8%)

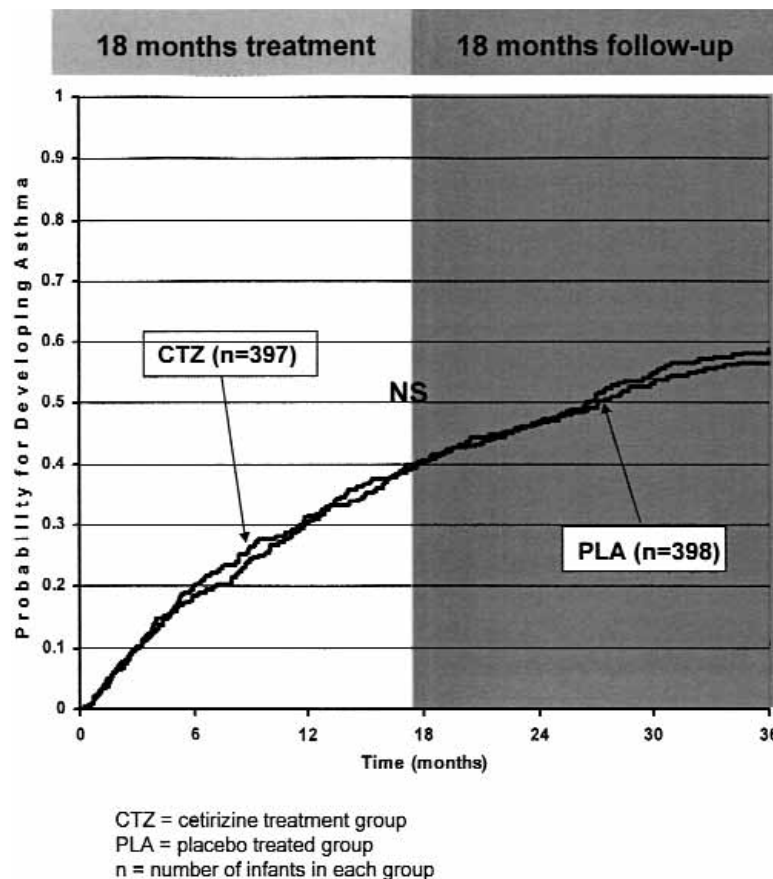


FIG 3. The percentages of infants in whom asthma developed, as mentioned in the text, are computed as the number of asthmatic patients at the end of 36 months of study divided by the total number of patients who entered the study. Because some patients left the study prematurely before being detected as potentially asthmatic, these percentages may underestimate the probability of becoming asthmatic during the study. The Kaplan-Meier curves used a correction to take account of the effect of early dropouts. Also shown is the occurrence of asthma by treatment group, either cetirizine or placebo, in the ITT population. CTZ, Cetirizine-treated group; PLA, placebo-treated group.

in whom asthma developed during the entire 36 months of follow-up (ie, 50.4% in the placebo group and 52.0% in the cetirizine group; $P = .707$, log-rank test). Fig 3 shows the probability of development of asthma over the 36-month follow-up period by using Kaplan-Meier estimates. Median time to onset of asthma was 27.1 and 26.5 months for the placebo and cetirizine groups, respectively. This apparently rather late median time to onset of asthma is due to the fact that children who already had asthma before recruitment into the study were excluded. In the placebo group 69.0% of the patients had at least 1 episode of wheeze or nocturnal cough compared with 69.6% in the cetirizine group.

A multivariate analysis (with the stepwise Cox model) was conducted to evaluate whether there was an association between baseline atopic characteristics and treatment. In the stepwise model the variables house dust mite, grass pollen, and treatment were related to the onset of asthma. After 18 months of treatment, there was a clear interaction with treatment for 2 aeroallergen sensitivities, grass pollen and house dust mite. After 36

months, this interaction was still significant for grass pollen but no more for house dust mite. This multivariate analysis adjusted the treatment effect to avoid any bias that might have resulted from an imbalance of egg sensitization at recruitment. Adjusting for IgE egg response had no significant effect on the models. Figs 4 and 5 show the Kaplan-Meier plots for both these aeroallergen sensitivities. In the sensitized children cetirizine delayed the occurrence of asthma compared with placebo, with this effect being of clinical relevance after 18 months of treatment. This effect is still clearly present throughout the 18-month posttreatment follow-up period for grass pollen-sensitized children, although the difference is less between cetirizine and placebo in the house dust mite-sensitized children. As in the previous report, after 18 months' treatment, no interactions were detected between treatment and sensitization at baseline for any of the other allergens (egg, milk, and cat).

During the 18-month posttreatment follow-up period, no statistically significant or clinically relevant differences were seen between patients in whom asthma devel-

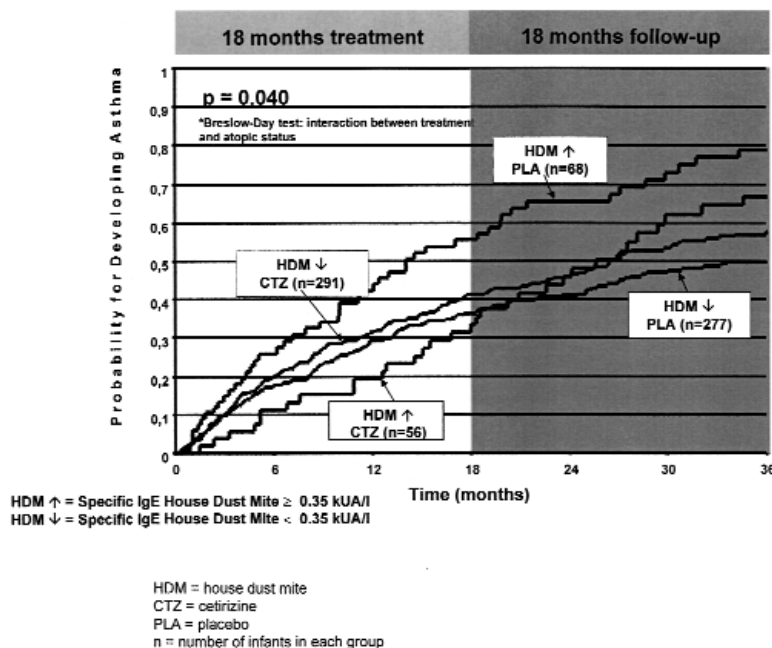


FIG 4. Percentages of infants in whom asthma develops, as mentioned in the text, are computed as the number of asthmatic patients at the end of 36 months of study divided by the total number of patients who entered the study. Because some patients left the study prematurely before being detected as potentially asthmatic, these percentages may underestimate the probability of becoming asthmatic during the study. The Kaplan-Meier curves used a correction to take account of the effect of early dropouts. Also shown is the occurrence of asthma by treatment in patients either sensitized or not to house dust mite at baseline. HDM, House dust mite; CTZ, cetirizine; PLA, placebo.

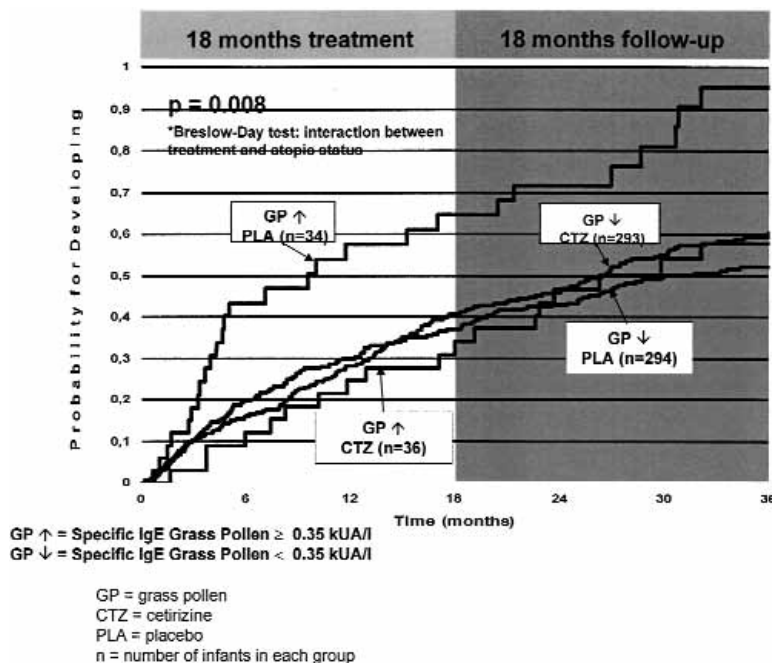


FIG 5. The percentages of infants in whom asthma develops, as mentioned in the text, are computed as the number of asthmatic patients at the end of 36 months of study divided by the total number of patients who entered the study. Because some patients left the study prematurely before being detected as potentially asthmatic, these percentages may underestimate the probability of becoming asthmatic during the study. The Kaplan-Meier curves used a correction to take account of the effect of early dropouts. Also shown is the occurrence of asthma by treatment in patients either sensitized or not sensitized to grass pollen at baseline. GP, Grass pollen; CTZ, cetirizine; PLA, placebo.

oped in the 2 treatment groups in relation to the use of asthma therapies except for sodium cromoglycate, with which, in the subgroup of patients with elevated grass pollen or house mite IgE levels at baseline, the consumption was considerably lower in the previously treated cetirizine group ($P = .035$, Mann-Whitney test). Patients were also classified as having active asthma if they had a diagnosis of asthma and had wheezed for at least 1 day in the last 12 months of the 3-year follow-up period. Analyses showed no statistically significant difference between placebo and cetirizine in the ITT population (34.4% vs 37.0% for placebo and cetirizine, respectively) for active asthma. However, analysis of active asthma in the subgroups defined by sensitization status at baseline showed very similar results to those observed for asthma at any time over the previous 3 years.

An analysis of the placebo group showed that the occurrence of active asthma was higher in patients sensitized to egg at baseline, whether they were still sensitized at 3 years (51.0%) or not (39.4%) compared with patients not sensitized during the study (26.3%). Only 4% not sensitized to egg at baseline had this sensitivity over the next 3 years. For house dust mite sensitivity, occurrence of active asthma was higher in patients who were already sensitized at baseline (62.2%) compared with patients not sensitized at baseline who became sensitized later during the study (42.6%) or patients who were never sensitized (23.1%). For grass pollen, the figures were 73.3%, 42.9%, and 26.0%, respectively.

The details of the evolution of atopic dermatitis in this study will be reported in detail in a separate article. However, during the course of the study, there was a continuous decline in the severity of eczema, as based on the SCORAD. There were no treatment effects observed on SCORAD. Nevertheless, the number of patients taking oral antihistamines as rescue medication was significantly less in the cetirizine group ($P = .03$). In patients with a high SCORAD index at baseline, there was a significant reduction in the percentage of days of use of moderate-to-potent corticosteroids in the cetirizine and placebo groups ($P = .014$). It is not possible to establish whether a positive effect of cetirizine on eczema was associated with a greater potential to prevent asthma because there was an overall trend toward improvement in eczema during the course of study in all treatment groups with all patterns of sensitivity.

Safety outcomes have been reported at length in another article.¹¹ However, basically, there were no significant differences for any adverse events or in QT and RR intervals between active and placebo therapy, other than for urticaria, in which fewer cases were reported in the cetirizine-treated group compared with the placebo-treated group during the treatment period; this effect disappeared during the posttreatment follow-up period. In addition, significantly fewer other antihistamines were used in the cetirizine-treated group compared with in the placebo-treated group during the treatment period, an effect that also disappeared during the follow-up period.

DISCUSSION

The evaluation of efficacy of cetirizine in preventing or delaying asthma during the 36 months of the study has shown a very similar outcome from that observed after the 18-month treatment period. Although the protective effect in house dust mite-sensitive individuals decreased, it was maintained in those with grass pollen sensitivity. It is striking that once the treatment was stopped, there was no rebound in asthma diagnosis, as was observed in relation to urticaria.¹² This emphasizes that the use of cetirizine in urticaria has a purely antihistaminic effect, but in the delay or prevention of asthma, a different mechanism could be hypothesized. This is the first study to suggest that in a subgroup of children with atopic dermatitis who were sensitized to grass pollen, it is possible to truly delay or perhaps even prevent the development of asthma.

The study has also highlighted very important risk factors for the development of asthma in patients with atopic dermatitis. Sensitizations to house dust mite, cat, and egg¹³ have been identified in the past, but this is the first study to show that grass pollen sensitization was also a predictor of subsequent asthma. It is interesting to note that those with early aeroallergen sensitization at recruitment who had evidence of persistent sensitivity on subsequent assessments were significantly more likely to have persistent (ie, active) asthma than those in whom sensitivity developed at a later stage. This has previously been shown in relation to egg sensitization¹⁴ but not for the aeroallergens.

Figs 4 and 5 show the considerable beneficial effect of cetirizine compared with placebo in infants with atopic dermatitis sensitized to grass pollen or house dust mite at recruitment but also a small and nonsignificant difference in favor of placebo in the nonsensitized group. The numbers of nonsensitized patients are large, and the small differences explain the lack of effect observed in the ITT population (Fig 3). In the subgroup of infants who had no evidence of specific IgE antibody at baseline to the 5 allergens, there was a slightly increased risk of subsequent asthma in cetirizine-treated compared with in placebo-treated patients. This was a small effect and was not considered to be clinically relevant. The nonsensitized group with clinically diagnosed atopic dermatitis was heterogenous in nature. Some may well not have been atopic at all and therefore have a totally different disorder. Others may have been sensitized to allergens for which they were not tested according to the protocol of this study, such as birch pollen, which would be particularly relevant to Scandinavian patients¹⁵ or perhaps another food. Thus it is highly improbable that there was any consistent adverse effect of cetirizine in the nonsensitized group.

It is interesting to speculate on the potential mechanism of action of cetirizine in delaying or preventing asthma in the atopic dermatitis subgroup sensitized to aeroallergens. Cetirizine has been shown to inhibit allergen-induced eosinophil trafficking in the skin, nose, lungs, and conjunctiva.⁹ Furthermore, it inhibits the aller-

gen-induced upregulation of the adhesion molecule intercellular adhesion molecule 1¹⁶ and IL-8 release from proinflammatory cytokine-stimulated human epithelial cells.¹⁷ Thus it is possible that the mechanism of action is through prevention of allergen-induced eosinophil and neutrophil trafficking into the airway as a key component of the inflammation that is associated with asthma and infantile wheezing.¹⁸ These potential mechanisms of action of cetirizine could explain a delay in the onset of asthma but do not indicate the way in which asthma would be totally prevented. It is likely that unless allergen sensitivity changes, which was not the case, continued aeroallergen exposure will eventually induce airway inflammation and thereby symptoms. The absence of an effect in relation to cat sensitization may be explained by the fact that 30% of cat-sensitized infants were still being directly exposed to cat allergen in the home. Furthermore, cat allergen is ubiquitous, being found in many environments outside the home.¹⁹ Cat allergen remains suspended in the air for very long periods by comparison with house mite allergen.²⁰ Both cat and house dust mite are likely to cause infants perennial exposure, whereas grass pollen exposure, for which the greatest therapeutic effect of cetirizine was observed, is only intermittent.

Because the ITT analysis showed no effect of the drug, it is clear that a future study will need to focus therapy on the specific subgroups of infants with atopic dermatitis who clearly benefited, mainly those with grass pollen sensitivity, house dust mite sensitivity, or both. However, the study has highlighted that there is the possibility of modifying the natural history of asthma with presymptomatic intervention. Additional studies will also include a more prolonged follow-up of this cohort to establish whether asthma has been truly prevented or merely delayed in onset. It will also be of interest to study whether cetirizine will have any effect in preventing asthma in children from other high-risk groups, such as those with a positive family history of atopy with or without evidence of allergic sensitization, those with rhinitis but without atopic dermatitis, or both. It will also be intriguing to establish whether cetirizine has any effect on early infant wheezing, given its demonstrable anti-inflammatory effects.

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