

Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: First results of ETAC®

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There is a common progression known as the allergic march from atopic dermatitis to allergic asthma. Cetirizine has several antiallergic properties that suggest a potential effect on the development of airway inflammation and asthma in infants with atopic dermatitis.

Methods. Over a two year period, 817 infants aged one to two years who suffered from atopic dermatitis and with a history of atopic disease in a parent or sibling were included in the ETAC® (Early Treatment of the Atopic Child) trial, a multi-country, double-blind, randomised, placebo-controlled trial. The infants were treated for 18 months with either cetirizine (0.25mg/kg b.i.d.) or placebo. The number of infants who developed asthma was compared between the two groups. Clinical and biological assessments including analysis of total and specific IgE antibodies were performed.

Results. In the placebo group, the relative risk (RR) for developing asthma was elevated in patients with a raised level of total IgE (≥ 30 kU/l) or specific IgE (≥ 0.35 kUA/l) for grass pollen, house dust mite or cat dander (RR between 1.4 and 1.7). Compared to placebo, cetirizine significantly reduced the incidence of asthma for patients sensitised to grass pollen (RR = 0.5) or to house dust mite (RR = 0.6).

However, in the population that included all infants with normal and elevated total or specific IgE (intention-to-treat – ITT), there was no difference between the numbers of infants developing asthma while receiving cetirizine or placebo. The adverse events profile was similar in the two treatment groups.

Discussion. Raised total IgE level and raised specific IgE levels to grass pollen, house dust mite or cat dander were predictive of subsequent asthma. Cetirizine halved the number of patients developing asthma in the subgroups sensitised to grass pollen or house dust mite (i.e. 20% of the study population). In view of the proven safety of the drug, we propose this treatment as a primary pharmacological intervention strategy to prevent the development of asthma in specifically sensitised infants with atopic dermatitis.

ETAC® Study Group*

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The prevalence of asthma, atopic dermatitis and hay fever has increased over the last three decades in many countries (1) and the economic burden of treating these diseases is considerable. So far, no intervention has been shown to alter the natural history of asthma and hay fever. It is known that exposure to high levels of allergen in early life is a major trigger (2), but attempts at prevention by allergen avoidance have produced conflicting results with no benefit at all (3), only transient (4) or, in the case of one study, a long lasting effect (5).

There is a strong association between atopic dermatitis and the subsequent development of asthma. Around 40% of infants with atopic dermatitis in early infancy will develop asthma at the age of three to four years (6). There are two studies (7, 8) reporting a pharmacological intervention to prevent the development of asthma. Both employed ketotifen, one in infants with atopic dermatitis and the other in infants with a family history of allergy and raised serum total IgE levels, both of which showed a significant reduction in the subsequent

prevalence of asthma. However, subject numbers were relatively small and there was no attempt made to associate this effect with sensitisation to specific allergen or other factors identified as risk factors for the development of the disease.

In asthma, airway inflammation is characterised by eosinophil recruitment and associated with ICAM-1 up-regulation in the respiratory epithelium, the endothelium and many inflammatory cells (9).

Cetirizine, a potent and selective antihistamine (10, 11, 12), is used extensively in both children and adults (13). It inhibits *in vivo* ICAM-1 expression in nasal and conjunctival epithelium during allergic inflammation (14, 15) and eosinophil recruitment in the skin, nose, eyes and lungs (16, 17).

The primary aim of the ETAC® (Early Treatment of the Atopic Child) study was to establish on the intention-to-treat (ITT) population whether an 18 month-cetirizine treatment could prevent the onset of asthma in young children with atopic dermatitis, when compared to placebo. However, it was anticipated that there may be no overall effect on pragmatically selected AD patients based on clinical criteria alone. Therefore, prior to breaking the study code, additional analyses based on specific allergic sensitivities and accounting for other confounding variables were also included in the protocol. A 30% reduction in the incidence of asthma was considered to be clinically relevant. Secondary parameters of efficacy included the severity of asthma and atopic dermatitis. The safety of long-term treatment with cetirizine in infants has also been evaluated.

This paper reports on the findings related to the primary end point for efficacy.

Methods

The study was co-ordinated by a Scientific Advisory Board (SAB) consisting of independent clinicians and scientists, who were not involved in the study as investigators and blind to the treatment randomisation. The SAB was involved in protocol design and in monitoring the safety, conduct, analysis and report of the study.

Study population

The target population were infants aged one to two years with active symptoms of atopic dermatitis for at least one month before enrolment. All the infants had to have at least one parent or sibling with a history of atopic disease (atopic dermatitis, allergic rhinitis or asthma). Excluded were infants with asthma, or with a history, beyond the age of six months, of one or more episodes of wheezing or nocturnal cough as well as any condition likely to obscure the diagnosis of asthma (18, 19).

Other exclusion criteria were: weight below the third percentile, chronic pulmonary disease of any type, severe neurological or psychological disorder, any third disease likely to interfere with the absorption, distribution, metabolism or elimination of the study drug, and participation in a clinical study within three months before randomisation. Furthermore, clinically relevant cardiac disease, any anomaly of the QT interval on ECG tracing, a history of sleep apnea in the subject or siblings, neonatal distress, prior treatment with medicines interfering with the immune system, prior desensitisation or immunotherapy, hypersensitivity to cetirizine or other piperazines or parabens also led to exclusion.

Study design

ETAC® was a prospective, randomised, double blind, parallel group and placebo-controlled study of cetirizine. Patients taking oral treatment for atopic dermatitis or other disease containing systemic corticosteroids, cromoglycate or antihistamines at screening were requested to stop these medications and return for baseline evaluations after a washout period. Topical therapy could be continued during the washout period. The length of the washout period depended on the type of specific medication used. At baseline, a detailed history was taken concerning the infant's atopic disease and related risk factors. The latter included the infant's environment and the family history of atopic diseases. The severity of atopic dermatitis was rated with the atopic dermatitis scale SCORAD (20). Follow-up visits were scheduled after one month, three months and thereafter every 13 weeks (i.e. three months) during the 18 month-treatment period. Between visits, the parents/legal guardians were contacted also by telephone. Study treatment lasted for 18 months. After the treatment period, patients entered a long-term follow-up period. The follow-up results are not available yet and will be reported later.

Parameters of efficacy

The primary end-point for efficacy was the onset of asthma, defined as three episodes of nocturnal cough with sleep disturbances or wheezing, separated by at least seven days, in a clinical setting where asthma is likely and conditions other than allergy have been excluded. All these symptoms were recorded by the parents/guardians on diary cards and validated by the investigator at the next visit.

All these data were calculated and reviewed before database lock by an independent Data Review Committee including SAB members.

Secondary parameters of efficacy included the severity of asthma, consumption of concomitant medi-

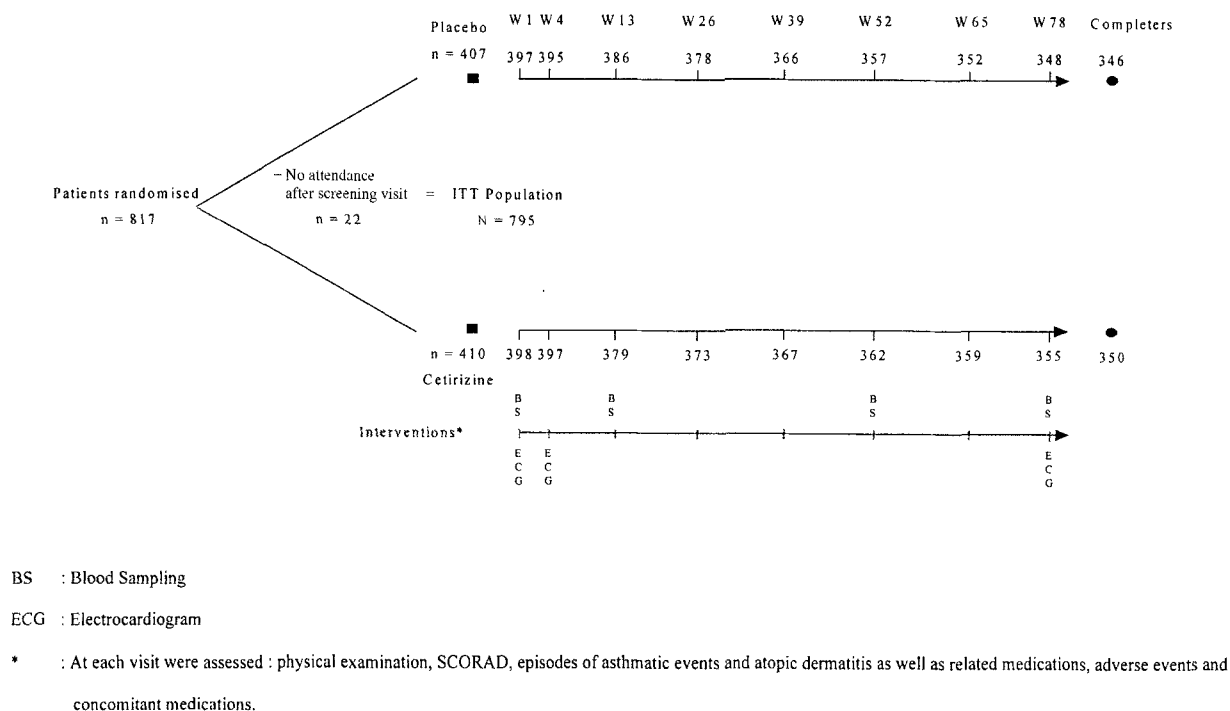


Diagram 1. Attrition diagram of the population over the 18-month treatment period, by treatment group.

cations and the severity of symptoms related to atopic dermatitis. These were evaluated according to the SCORAD score. In order to guarantee the homogeneity of the atopic dermatitis evaluation, all investigators were trained before the study on the use of this scale and their performances were compared with the scoring of expert dermatologists (21).

Serum total and specific (grass pollen, cow's milk, egg, house dust mites and cat dander) IgE antibody levels were determined using the Pharmacia CAP® system (Pharmacia & Upjohn, Uppsala, Sweden). These analyses were made at baseline, and after 3, 12 and 18 months of treatment by a central laboratory (Institut Pasteur - Bio Contract Research - Lille, France) according to manufacturer instructions and routine clinical laboratory performances. Total eosinophil counts were determined at the same times.

Safety parameters

At each visit, the atopy status, any concurrent illnesses, concomitant medications and procedures were recorded. Patients underwent a physical examination, including the measurement of vital signs. Analyses of blood and urine samples including SMAC (System Multiple Analysis Chamber along with transaminases) and immunochemistry parameters (see above), were performed by the central laboratory.

A six-lead ECG was recorded at baseline, after 1 and 18 months of treatment. A minimum of ten QRS complexes had to be recorded at a paper speed of 50 mm/s on lead DII to allow an accurate measurement of the QT interval. All ECG recordings were read by a single cardiologist. Timings for the various interventions are mentioned in Diagram 1.

Adverse events were recorded by the parents/legal guardians on diary cards and discussed with the investigator at each visit. Serious adverse events had to be reported immediately to the sponsor and Regulatory Authorities and Ethics Committee, if appropriate.

Counselling

Parents/legal guardians were carefully counselled at the beginning of the study and during the treatment period about the risk factors involved in the onset of asthma. In particular, their attention was drawn to environmental factors, such as food allergens, pollen, house dust, tobacco smoking, air pollution, gas cookers, wall-to-wall carpeting, etc. The investigators gave specific advice regarding allergen avoidance on a case-by-case basis. A newsletter, including practical advice about the management of atopic patients and the control of risk factors, was distributed periodically to all investigators for passing on to the parents/guardians.

Study medications, randomisation, blinding compliance and rescue medication

UCB S. A. (Brussels, Belgium), provided 20 ml bottles of an oral solution of cetirizine (10 mg/ml) and matching placebo, similar in appearance and taste. The recommended study dosage was 0.25 mg cetirizine/kg b.i.d. In order to minimise calculation errors, a table of correspondence between body weight, dose and number of drops per intake was provided to each investigator. Treatment codes (A or B) were allocated to treatment numbers according to a randomisation list by blocks of 2, stratified by centre, created using a validated SAS® computer software, version 6.04. Treatments (placebo, cetirizine) were assigned to treatment codes independently by the UCB clinical supply unit. At each site, patients were assigned a treatment number in ascending order of their entry into the study.

Individual code envelopes were prepared for the investigators, to be opened only in case of emergency. The study code was kept secret throughout the study and broken only after the final statistical analysis plan was approved and the database frozen. Compliance was assessed by the investigators according to the entries in the diary cards and by quantification of unused study medication.

During a specific pre-trial investigators training, the recommendations of the Paediatric Consensus Group for asthma (22) were explained and rescue medications for atopic dermatitis were suggested. All concomitant medications had to be recorded by the parents/legal guardians on the diary card and by the investigator in the case report form.

Ethics, stopping rules, and regulatory compliance

Authorised ethics review committees at all involved sites approved the study protocol and amendments. Parents/legal guardians were informed about the study in writing and during an interview with the investigators or their staff, written informed consent was obtained for each infant from the parents/legal guardians prior to entry into the study. At any time in the study, a patient could be dropped for the following reasons: any safety issue in the opinion of the investigator, withdrawal of consent, lack of co-operation from the child or family.

The study was approved by or brought to the attention of the national/local regulatory authorities as appropriate in each country. Qualified monitors visited each site to verify source documents. The study was conducted in accordance with EC guidelines on Good Clinical Practice (July 1991) and the Declaration of Helsinki (September 1989).

Sample size and statistical methodology

Sample size was based on an expected cumulative incidence of asthma in 40% of children in the placebo group after 18 months of treatment. A decrease of 30% of the incidence, i.e. an incidence of 28% in the cetirizine group, was considered as clinically relevant. In order to have 80% power to demonstrate such a difference, two-tailed at the 5% level of significance, 500 infants would have to be enrolled in the study. Taking into account dropouts, 700 patients had to be randomised.

Computations were performed using the SAS® package, version 6.12. Statistical tests were performed two-tailed at the 5% level of significance. The difference between the two treatment groups in the cumulative incidence of asthma was evaluated on the ITT population using the Log-Rank test. Cumulative incidence curves were computed using the Kaplan-Meier estimate and displayed by treatment group. Relative risk ratios and their 95% CI were calculated based upon the incidence of asthma during the entire treatment period. The frequency of patients with adverse event was compared in the two treatment groups using the Fisher Exact test.

Results

The number of infants enrolled in the study between February 1994 and December 1995 ($n = 817$) exceeded the number planned ($n = 700$) and the overall dropout rate over the 18-month treatment period, was low ($n = 121$). The study population is described in the flow chart (Diagram 1) and in Table 1. The baseline characteristics of the two treatment groups, including the mean SCORAD values, family history of atopy and environmental factors were comparable. In addition, the proportion of patients with elevated IgE antibodies (total or specific), was similar in both treatment groups, except for sensitisation to egg, which was more frequent in the placebo group (data not shown).

Infants in the placebo group with raised baseline levels of serum total IgE (≥ 30 kU/l) or specific IgE antibodies (≥ 0.35 kUA/l) had an increased relative risk of developing asthma (Table 2). This increase was observed for all measured IgE antibodies and was significant for total IgE, grass pollen, house dust mite and cat dander allergens.

Overall there was no statistically significant difference between the numbers of children who developed asthma when receiving cetirizine (150/398; 37.7%) or placebo (151/397; 38.0%) (Table 3).

No difference was noted in the subgroups of specific asthmatic patients defined as wheezers only or asthma onset date at least three months after inclusion.

Table 1. Patient characteristics

	Placebo	Cetirizine	Total
Screened *			830
Enrolled in the study at V1	407	410	817
ITT Population =	397	398	795
Study completed until V8	346	350	696
Study prematurely discontinued	51	48	99
For therapeutic reasons (AEs)	15	11	26
For non-therapeutic reasons	36	37	73
Major violators†	84	86	170
Age (months) at inclusion			
Mean ± St.dev.	17.2 ± 4.1	16.8 ± 4.2	17.0 ± 4.1
Median	16.5	15.8	16.1
Min – Max	10–25	11–28	10–28
Gender			
Boys	248 (62.5%)	246 (61.8%)	494 (62.1%)
Girls	149 (37.5%)	152 (38.2%)	301 (37.9%)
Scorad at baseline			
Mean ± St.dev.	25.1 ± 14.0	24.9 ± 14.7	25.0 ± 14.4
Median	23.1	22.7	23.1
Min – Max	0–80	0–80	0–80
Asthmatic mother	79 (19.9%)	71 (17.8%)	150 (18.9%)
Asthmatic father or mother	157 (39.6%)	150 (37.7%)	307 (38.6%)
Environmental factors at baseline			
Industrial pollution	185 (46.6%)	171 (43.0%)	356 (44.8%)
Pets	141 (35.5%)	144 (36.2%)	285 (35.9%)
Exposed to tobacco smoke	156 (39.3%)	160 (40.2%)	316 (39.8%)

ITT : Intention-to-treat

* : The total number of patients considered for the trial has not been recorded.

= : 22 patients were excluded from ITT population (lack of follow-up data).

‡ : Major violations: – code breaking or loss of code envelopes (n = 24)
 – discontinuation for non-therapeutic reasons (e.g. lost to follow-up, ...) (n = 73)
 – non compliance with timing schedule (n = 56)
 – asthma symptoms before inclusion (n = 21)
 – age at inclusion < 11 months or > 25 months (n = 5)

However, analysis of the subgroups based on immunological parameters showed statistically significant differences of high clinical relevance. (Table 3; Figs. 1, 2).

Infants receiving cetirizine, who began the study with raised baseline levels of total IgE (≥ 30 kU/l) or specific IgE antibodies (≥ 0.35 kUA/l) had a reduced risk of developing asthma compared with those infants with raised baseline IgE antibodies, who received placebo.

This reduction was observed for all measured IgE antibodies and was significant for grass pollen ($P = 0.002$) and house dust mite ($P = 0.005$), either alone or combined (Figs. 1, 2). The relative risk for developing asthma associated with raised total eosinophils (> 0.7 giga/l) was 1.4 (95% CI: [1.0; 1.9]). In infants with raised total eosinophils, cetirizine did not significantly decrease the relative risk for developing asthma (RR = 0.9, 95% CI: [0.6; 1.3]).

Table 2. Occurrence of asthma by baseline atopic characteristics (placebo ITT population (n = 397))

	Normal (%)	Elevated (%)	RR for developing asthma in presence of elevated marker 95% CI]	Log-Rank Test p value
Total IgE (PRIST)*	62/185 (33.5)	75/172 (43.6)	1.3 [1.0 ; 1.7]	0.027
IgE Grass pollen (GX1)*	103/294 (35.0)	20/34 (58.8)	1.7 [1.2 ; 2.3]	< 0.001
IgE HDM (D1)*	96/277 (34.7)	35/68 (51.5)	1.5 [1.1 ; 2.0]	0.005
IgE Cat dander (E1)*	81/244 (33.2)	32/68 (47.1)	1.4 [1.0 ; 1.9]	0.032
IgE Egg (F1)*	43/140 (30.7)	55/140 (39.3)	1.3 [0.9 ; 1.8]	0.152
IgE Milk (F2)*	82/228 (36.0)	52/127 (40.9)	1.1 [0.9 ; 1.5]	0.250
IgE HDM+Grass Pollen	82/249 (32.9)	44/82 (53.7)	1.6 [1.2 ; 2.1]	<0.001
Eosinophil count	88/252 (34.9)	30/63 (47.6)	1.4 [1.0 ; 1.9]	0.066

ITT : Intention-to-treat

RR : Relative risk

CI : Confidence interval

() * : Pharmacia & Upjohn Diagnostics references

HDM : House dust mite

Elevated values: Total IgE: ≥ 30 kU/l, Specific IgE: ≥ 0.35 kUA/l, Eosinophils: > 0.7 giga/l

Table 3. Occurrence of asthma by treatment in the ITT population

	Placebo(%)	Cetirizine (%)	RR for developing asthma when cetirizine treated [95% CI]	Log-Rank test p value
ITT population	151/397 (38.0)	150/398 (37.7)	1.0 [0.8 ; 1.2]	0.973
Subgroups with elevated IgE or eosinophils at baseline				
Total IgE (PRIST)*	75/172 (43.6)	64/168 (38.1)	0.9 [0.7 ; 1.1]	0.391
IgE Grass pollen (GX1)*	20/34 (58.8)	10/36 (27.8)	0.5 [0.3 ; 0.9]	0.002
IgE HDM (D1)*	35/68 (51.5)	16/56 (28.6)	0.6 [0.3 ; 0.9]	0.005
IgE Cat dander (E1)*	32/68 (47.1)	26/64 (40.6)	0.9 [0.6 ; 1.3]	0.610
IgE Egg (F1)*	55/140 (39.3)	38/122 (31.2)	0.8 [0.6 ; 1.1]	0.292
IgE Milk (F2)*	52/127 (40.9)	35/114 (30.7)	0.7 [0.5 ; 1.0]	0.140
IgE HDM+Grass pollen	44/82 (53.7)	26/76 (34.2)	0.6 [0.4 ; 0.9]	0.006
Eosinophil count	30/63 (47.6)	32/75 (42.7)	0.9 [0.6 ; 1.3]	0.674

ITT : Intention-to-treat

RR : Relative risk

CI : Confidence interval

() * : Pharmacia & Upjohn Diagnostics references

HDM: House dust mite

Elevated values: Total IgE: ≥ 30 kU/l, Specific IgE: ≥ 0.35 kUA/l, Eosinophils: > 0.7 giga/l

There were no significant differences in the adverse event (AE) profiles between groups except for urticaria (16.1% versus 5.8%, $P < 0.001$) which was less frequent in the cetirizine group. The frequency of agitation, appetite increase and ECG abnormali-

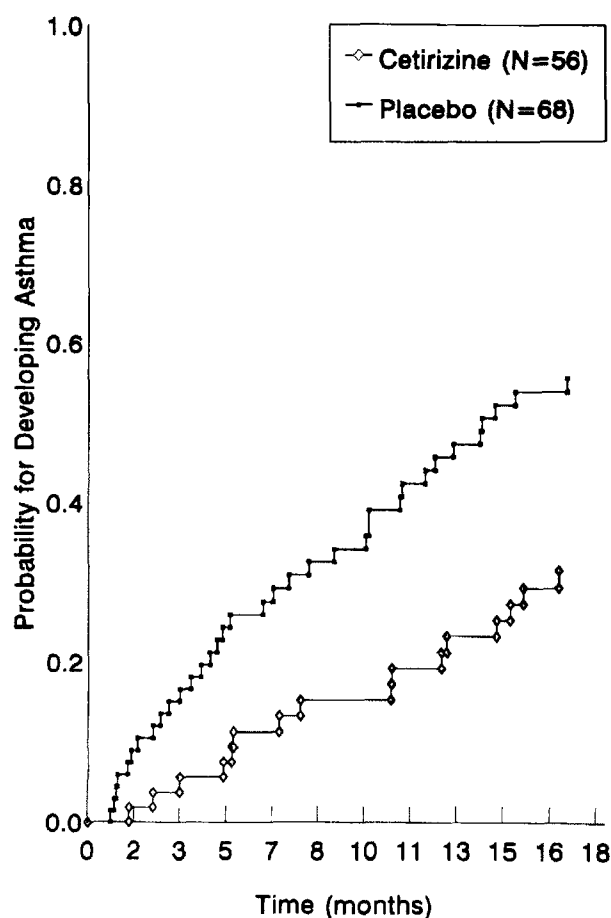


Fig. 1. Occurrence of asthma by treatment in patients sensitised to house dust mite at baseline.

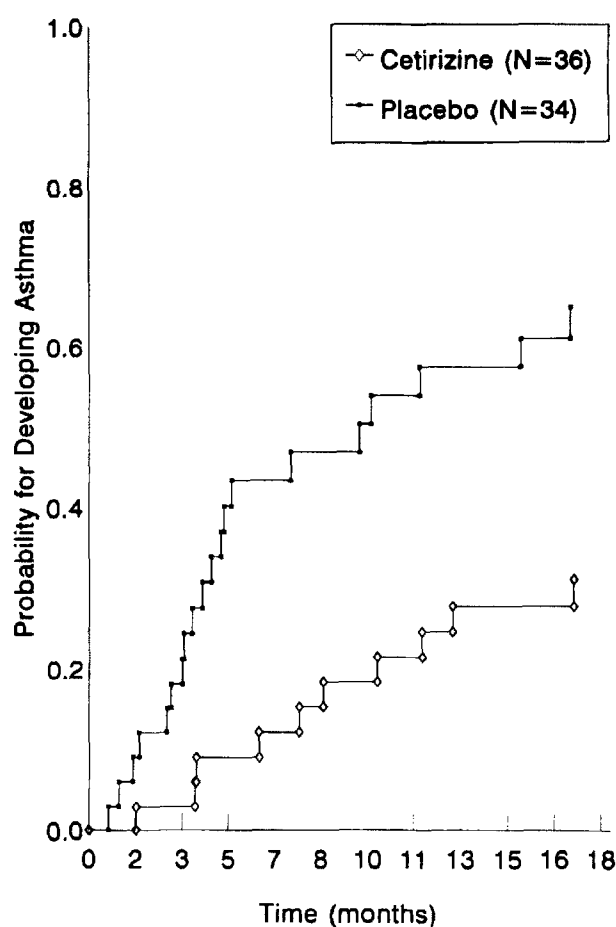


Fig. 2. Occurrence of asthma by treatment in patients sensitised to grass pollen at baseline.

ties (QT interval prolongation) were below 1% in both groups (Table 4). The number of serious adverse events recorded during the study was 106. Only one was considered by the SAB to be possibly related to cetirizine. The child had raised transaminases levels at inclusion (ASAT 48 UI/l, ALAT 54 UI/l). After five weeks of cetirizine treatment, the values reached a peak (ASAT 1100 UI/l, ALAT 1300 UI/l). One week after withdrawal, the values were 146 and 594, respectively, and returned to 61 and 67 after one month. It is worth noting that all other biological values were within normal ranges (CRP, virology, etc.) and the child remained asymptomatic throughout observation and remained healthy afterwards.

Concomitant use of oral macrolides by 30.7% of children in either group did not affect either hepatic safety parameters (ASAT and ALAT) or QT interval values.

Discussion

The study shows that early treatment with cetirizine (initiated between one and two years of age) halved the number of children developing asthma, when

they were suffering from atopic dermatitis and were sensitised (raised specific IgE antibody levels ≥ 0.35 kUAl) to grass pollen or house dust mite. This constituted 20% of the total atopic dermatitis population recruited into the study.

ETAC® has already generated a wealth of data, which is aiding our understanding of the evolution of atopy. The high degree of standardisation of patient recruitment and careful monitoring of the study by the independent SAB and the ETAC® Team ensured that Good Clinical Practice requirements were met. The low dropout rate was due to the efforts of the investigators and monitors but especially to the commitment of parents/legal guardians.

Inclusion criteria were pragmatic and based on simple clinical assessment: atopic dermatitis was defined using commonly used standard criteria (23, 24) with a requirement that at least one parent or sibling was atopic (allergic rhinitis, atopic dermatitis or asthma) (25). However, analysis of the baseline data shows that 69.9% of the participants were atopic as defined in terms of immunoreactivity by raised total IgE or specific IgE antibody levels to one of five allergens (26). Due to the fact that in-

Table 4. Adverse events of interest with antihistamines

Adverse Events	Placebo % of patients experiencing at least one adverse event	Cetirizine % of patients experiencing at least one adverse event
Abdominal pain	4.3	4.3
Agitation	0.5	0.3
Allergic reaction	13.4	9.1
Anorexia	4.0	3.3
Appetite increased	0.3	0.5
ECG abnormalities	0.3	0.0
Fatigue	1.3	3.3
Hepatic enzymes increased	1.8	1.3
Hyperkinesia	2.5	1.3
Insomnia	5.3	8.8
Laryngitis	9.3	7.3
Somnolence	2.0	2.3
Urticaria	16.1	5.8
Vaccination complication	5.5	3.3

ECG: Electrocardiogram

infants were recruited on the basis of atopic dermatitis rather than sensitisation – hence introducing a heterogeneity within the cohort – it is not surprising that different baseline characteristics led to different outcomes for the development of asthma.

The present study is the first to show that sensitisation to grass pollen in such young infants is a powerful predictor of the future onset of asthma. It confirms previous reports indicating that pre-existing sensitisation to house dust mite (27) or cat dander allergen (28) or raised serum total IgE strongly predict the subsequent development of asthma. Raised blood eosinophil count just failed to reach significance as a predictor.

Sensitisation to egg in this population of infants with atopic dermatitis is not shown to be a significant risk factor for asthma, unlike the findings of Burr and Merrett (29) who studied children with and without atopy. Milk sensitisation has a weak association with subsequent asthma. This finding agrees with previous studies and may be due to the fact that milk sensitivity tends to be a problem in early infancy, which usually resolves after two to three years of age.

Cetirizine significantly reduced the risk of subsequent asthma in infants with the strongest predictors for developing it. For these infants who were sensitised to grass pollen or house dust mite, the relative risk of subsequent asthma was reduced to 0.5 and 0.6 respectively. No effect was seen in infants sensitised to cat dander allergen. We had already established that individuals in this study who were allergic to cat dander continued to keep their pet (26), thus overwhelming the effect of any pharmacological intervention. In the ITT population, the adminis-

tration of cetirizine compared with placebo conferred no advantage in terms of the number of children developing asthma during the study.

More and more evidence shows that eosinophils play a pivotal role in the development of airway inflammation, and hence, asthma. Eosinophilia has been described in broncho-alveolar lavage from young children with asthma (30). While it is clear that antihistamines do not play a major role in the treatment of asthma, cetirizine – which prevents eosinophil trafficking – has the potential to prevent the evolution of the disease. This hypothesis is substantiated by the present findings. Allergic asthma has been prevented in infants at high risk, who have atopic dermatitis and evidence of aeroallergen (grass pollen or house dust mite) sensitisation. As early house dust mite sensitivity in childhood asthma is associated with persistent symptoms in long term follow-up (31), it is likely that this intervention will be highly cost-effective.

This large trial in infants has shown that cetirizine is a safe product. Ten overdoses were observed, but only two were with cetirizine (up to a single intake of 180 mg) (32). In no case were related serious adverse events observed. Safety is confirmed even when cetirizine is taken in association with macrolide antibiotics. Therefore, the much-publicised concern about antihistamines having an impact on QT interval is clearly not a generic effect for this group of drugs.

This double-blind trial of the use of cetirizine in infants with atopic dermatitis shows that it successfully prevents asthma in infants with evidence of sensitivity to either grass pollen or house dust mite. In view of the proven safety of this drug, it is proposed as a primary intervention treatment to prevent the development of asthma in eczematous infants sensitised to these allergens.

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