

Long-term treatment with cetirizine of infants with atopic dermatitis: A multi-country, double-blind, randomized, placebo-controlled trial (the ETACTM trial) over 18 months

Diepgen TL on behalf of the ETACTM Study Group. Long-term treatment with cetirizine of infants with atopic dermatitis: A multi-country, double-blind, randomized, placebo-controlled trial (the ETACTM trial) over 18 months.

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H₁-receptor antagonists are considered central to the treatment of atopic dermatitis (AD)-associated pruritus and are widely used in the treatment of AD despite a lack of double-blind, randomized clinical trials. In this study we analyzed the effects of the long-term use of cetirizine on the severity, natural history, and treatment of AD. In the prospective, multi-country, double-blind, randomized, placebo-controlled Early Treatment of the Atopic Child (ETACTM) study, 817 infants (12–24 months of age) who suffered from AD at study entry and with a history of atopic disease in a parent or sibling were treated for 18 months with either cetirizine (0.25 mg/kg) or placebo twice daily. All concomitant medications for the treatment of AD were allowed but had to be recorded by the investigator in the case report form; the concomitant use of H₁-antihistamines was discouraged. The primary end-point for efficacy was the onset of asthma. Secondary parameters of efficacy, however, were the consumption of concomitant medications for AD (topical and systemic treatment) and the severity of symptoms related to AD, which was rated with the AD scale, SCORAD. The severity of AD, as measured by SCORAD, decreased significantly ($p < 0.001$) over the study period (18 months) in both groups. Other oral H₁-antihistamines were significantly more often used in the placebo group than in the cetirizine group (24.9% vs. 18.6%, $p = 0.03$). The number of infants who developed urticaria during the study period was significantly lower with cetirizine treatment (placebo group: 16.2%; cetirizine group: 5.8%; $p < 0.001$). For the treatment of AD, mild topical corticosteroids (class I, e.g. hydrocortisone) were used in 41.6% of the patients (placebo group 41.6%, cetirizine group 41.7%) and moderate-to-potent topical corticosteroids (class II, III, IV) in 55.0% (respectively 56.4% and 53.5%). The duration of the use of topical moderate-to-potent corticosteroids differed between the cetirizine group and the placebo group (mean percentage of days: placebo 25.2, median 2.4; cetirizine mean 18.8, median 0.95 $p = 0.067$, Mann–Whitney test, not statistically significant). In sub-groups of infants with a SCORAD of ≥ 25 , this cortico-sparing effect was statistically significant (placebo 35.1 vs. 25.8 in the cetirizine group; $p = 0.014$, Mann–Whitney test). In conclusion, in view of the proven safety of cetirizine, the use of this drug might help to reduce the duration and the amount of moderate-to-strong topical corticosteroids used in the treatment of infants and children with AD. However, further studies designed with the primary end-point of AD are clearly indicated to confirm the benefits of the use of H₁-antihistamines in the management of AD.

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Key words: atopic dermatitis; asthma; treatment; cetirizine; antihistaminics; corticosteroids; urticaria; IgE

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Atopic dermatitis (AD) is a chronic inflammatory eczematous skin disease often seen in children and young adults with a personal or family history of atopy (asthma, allergic rhinitis, AD) (1). There has been an increase in the prevalence of atopic disorders (AD, allergic rhinitis, allergic asthma) over the last decades (2). AD often

begins in the first 2 years of life and achieves the highest morbidity scores on disability measures when compared with other skin diseases (3). Data from a national British cohort study (the NCDS) suggest a 10-year clearance rate of around 50% (4). Additionally, the economic burden of treating AD is considerable (5).

The pathogenesis of AD is still obscure, and the management of this chronic disease difficult. Antihistamines are widely used in the treatment of AD despite a lack of objective evidence based on randomized, clinical trials. Therefore randomized, clinical trials are lacking to assess whether the use of H₁-antihistamines could be of any benefit in the management of AD.

Cetirizine, a potent and selective antihistamine (6–8), is used in both children and adults (9). It inhibits *in vivo* intracellular adhesion molecule-1 (ICAM-1) expression in nasal and conjunctival epithelium during allergic inflammation, and eosinophil recruitment in the skin, nose, eyes, and lungs (10–13).

Here, we report the findings of the first prospective, multi-country, double-blind, randomized, placebo-controlled study where cetirizine was given over a time-period of 18 months to infants with AD. The primary aim of the ETAC[®] study (Early Treatment of the Atopic Child) was to establish whether 18 months of treatment with cetirizine could prevent the onset of asthma in young children with AD, when compared to placebo (14). Secondary parameters of efficacy included the severity of AD and asthma, and the concomitant medication. The safety of long-term treatment with cetirizine in infants has also been evaluated (15).

This article reports on the findings related to AD during the 18-month period.

Subjects and methods

The study was co-ordinated by a Scientific Advisory Board (SAB), the members of which

were not involved in the study as investigators and blind to the treatment randomization. The SAB was involved in protocol design and in monitoring the safety, conduct, analysis, and reporting in the study.

Study population

In 12 European countries and Canada, infants 1–2 years of age, with active symptoms of AD for at least 1 month before inclusion and at least one parent or sibling with a history of AD, allergic rhinitis, or asthma, were enrolled. Written, informed consent was obtained from their parents or guardians. Patients were enrolled in dermatological or pediatrician clinical centers (in total 56 centers). Infants with asthma, or with a history (beyond the age of 6 months) of one or more episodes of wheezing or nocturnal cough as well as any conditions that might obscure the diagnosis of asthma (14), were excluded from the study. Further exclusion criteria were: weight below the third percentile, chronic pulmonary disease, severe neurologic or psychologic disorder, any third disease likely to interfere with the study drug, clinical relevant cardiac disease, any anomaly of the Q–T interval on electrocardiogram (ECG) tracing, a history of sleep apnea in the subject or siblings, neonatal distress, prior desensitization or immunotherapy, prior treatment with medicines interfering with the immune system, hypersensitivity to cetirizine or other piperazines or parabens, and participation in a clinical study within 3 months before randomization.

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Study design

ETAC was a prospective, randomized, double-blind, parallel-group study comparing cetirizine with a placebo. Patients taking systemic corticosteroids, cromoglycate or oral antihistamines for any reason at screening were requested to stop these medications and return for baseline evaluations after a washout period. Topical therapy could be continued.

At baseline, a detailed history was taken concerning the infant's atopic disease and related risk factors (including the child's environment, such as domestic animals, smoking habits at home, dietary risk factors in infancy, the presence of a gas cooker in the kitchen, the type of floor covering in the child's bedroom, the distance from a source of industrial pollution).

The severity of AD was rated with the AS scale, SCORAD (16). All investigators were trained before the study on the use of SCORAD to obtain a high homogeneity of severity evaluation (17).

The infants received placebo or 0.25 mg of cetirizine/kg twice daily for 18 months. Twenty-millilitre bottles of an oral solution of cetirizine (10 mg/ml) and matching placebo (similar in appearance and taste) were provided by UCB S.A. Pharma Sector (Brussels, Belgium). All concomitant medications were allowed but had to be recorded by the parents/guardians on the diary card and by the investigator in the case report form. However, investigators were discouraged from using antihistamines except when considered absolutely necessary.

Follow-up visits were scheduled after 1 month, 3 months, and thereafter every 13 weeks during the 18-month treatment period. Between visits,

the parents/guardians were contacted additionally by telephone. At each visit, infants underwent a physical examination where the status of atopy, the severity of AD according to SCORAD, the consumption of concomitant topical and systemical medications, and the occurrence of any concurrent illnesses, were recorded.

Additionally, blood and urine samples were taken at baseline, and after 3, 12, and 18 months of treatment. On these dates, total and specific immunoglobulin E (IgE) [grass pollen (GX1), cow's milk (F2), egg (F1), house dust mites (D1), and cat (E1)] and eosinophil counts were determined (IgE antibody levels by using the Pharmacia CAP system; Pharmacia, Uppsala, Sweden). Additional biological parameters and ECG were investigated (14,15,18). Any events occurring during the 18-month study period, including potential side-effects (adverse events), were carefully recorded by the parents/guardians on diary cards and discussed with the investigator at each visit; serious adverse events (e.g. any hospitalization) had to be reported immediately.

Parents/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. A newsletter including practical advice about the management of AD and the control of risk factors was distributed periodically to all investigators for passing on to the parents/guardians. Written, informed consent was obtained for each infant from the parents/legal guardians prior to entry into the study. The study was conducted in accordance with EC guidelines on Good Clinical Practice and the Declaration of Helsinki.

Table 1. Baseline characteristics of the patients

Characteristics	Placebo	Cetirizine	Total
ITT population (n)	397	398	795
Study completed until V8 (n)	346	350	696
Age (months)	17.2±4.1	16.8±4.2	17.0±4.1
Male (%)	62.5	61.8	62.1
SCORAD at baseline			
Mean ± SD	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
Total IgE (≥30 kU/l)	48.2%	47.1%	47.6%
Specific IgE			
Cat (≥35 kUA/l)	21.8%	20.4%	21.1%
Grass pollen (≥35 kUA/l)	10.4%	10.9%	10.7%
HDM (≥35 kUA/l)	19.7%	16.1%	17.9%
Milk (≥35 kUA/l)	35.8%	32.5%	34.1%
Egg (≥35 kUA/l)	50.0%	41.5%	45.6%
Total eosinophils (>0.7×10 ⁹ /l)	17.4%	21.8%	19.6%

HDM, house dust mite; IgE, immunoglobulin E; ITT, intention to treat; SD, standard deviation.

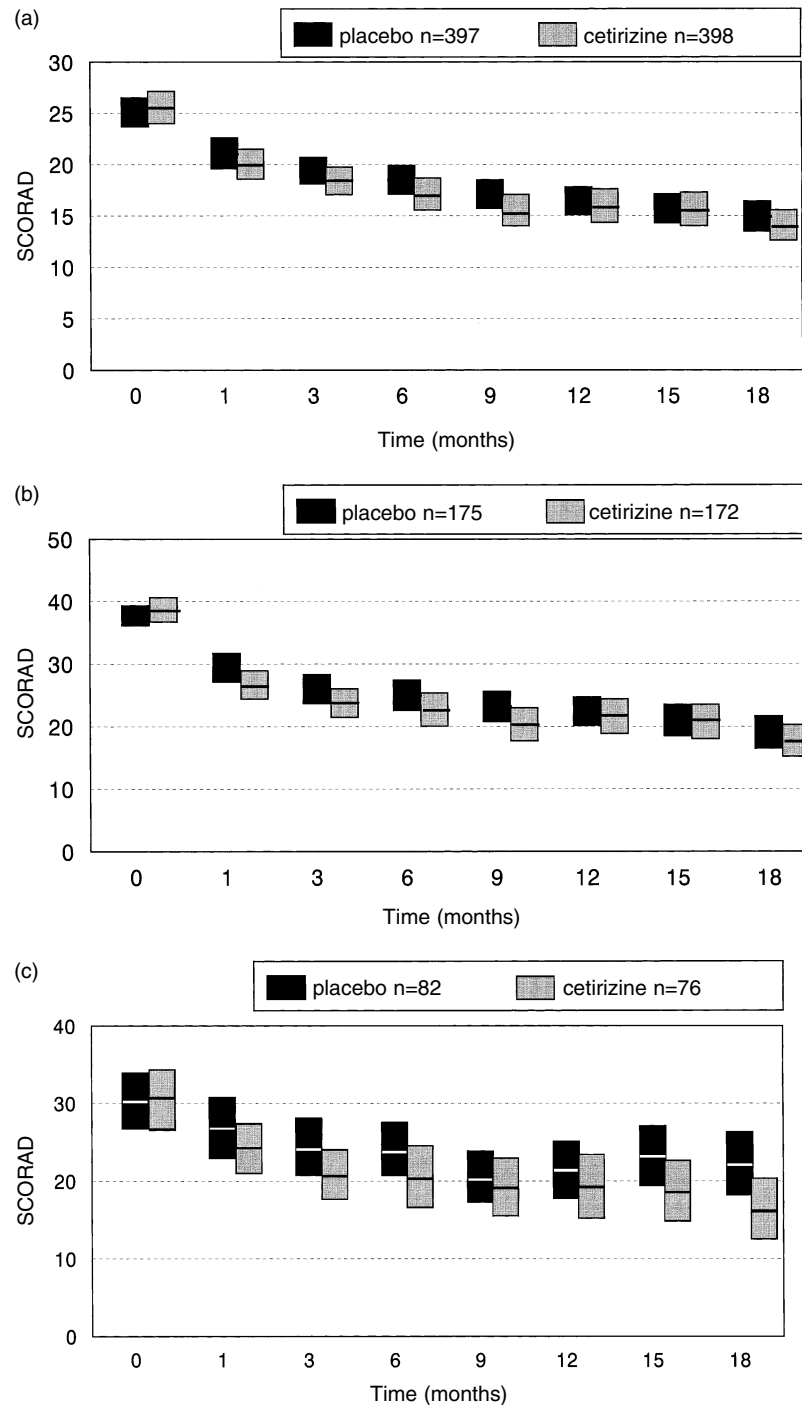


Fig. 1. Severity of atopic dermatitis (AD) according to the SCORAD index in infants treated with placebo (n=397) or cetirizine (n=398) over 18 months (a). Mean values and 95% confidence intervals are shown. Additionally, the data for infants with more severe AD at baseline (SCORAD index at baseline ≥ 25) (b), and for infants sensitized to grass pollen or house dust mite (c) are presented.

Parameters of efficacy, sample size, and statistics

The primary aim for efficacy was a reduction of 30% in the incidence of asthma during the 18-month time-period of the study. Sample size calculation was based on an expected 40% cumulative incidence of children developing

asthma during the 18-month treatment period in the placebo group and 28% in the cetirizine group. According to these assumptions, at least 500 patients had to be enrolled in the study. The results on asthma have been reported previously (14). Secondary parameters of efficacy included

Table 2. Topical and systemic medications used for the treatment of atopic dermatitis during the 18-month study period

Treatment	Placebo (n=397) No. (%)	Cetirizine (n=398) No. (%)	p-value (chi-square)
Topical medications			
Emollients	302 (76.1)	306 (76.9)	0.79
NSAI creams	55 (13.9)	56 (14.1)	0.93
Tar	57 (14.4)	57 (14.3)	0.99
Local antibiotics/antiseptics	100 (25.2)	84 (21.1)	0.17
Local steroids: class I	165 (41.6)	166 (41.7)	0.97
Local steroids: classes II, III, IV	224 (56.4)	213 (53.5)	0.41
Systemic medications			
Oral H ₁ -antihistaminics	99 (24.9)	74 (18.6)	0.03
Oral antibiotics	47 (11.8)	41 (10.3)	0.49

The percentages are shown of patients with at least one concomitant medication in the placebo group (n=397) and in the cetirizine group (n=398)

any reduction in the severity of symptoms related to AD. These results are reported below.

Variables were tested using parametric and non-parametric tests, as appropriate. All statistical tests were performed two-sided at the 5% level of significance. No adjustment for multiplicity was applied. All analyses were performed using the SAS[®] package, version 6.12 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 830 infants with AD were screened for enrolment into the study between February 1994 and December 1995, out of which 795 infants were treated (397 with placebo, 398 with cetirizine) and had follow-up information collected. Over the 18-month treatment period, 51 infants in the placebo group and 48 in the cetirizine group dropped out. The baseline characteristics of the two groups, including the severity of AD according to the SCORAD index (25.1 vs. 24.9), the proportion of patients with

elevated IgE antibodies (total or specific), and the percentage of eosinophils $> 0.7 \times 10^9/l$ were similar in both treatment groups (Table 1).

During the 18-month study period the severity of AD decreased steadily without any statistically significant differences between the placebo and the cetirizine group (Fig. 1). Patients evolved from an average SCORAD index at baseline visit of 24.9 to 15.2 (cetirizine) and 25.1 to 15.7 (placebo) at the last visit (Fig. 1a). At the start of the study, a higher SCORAD index (≥ 25 points) was measured in 347 (43.7%) out of 795 infants. In these children with a more severe clinical manifestation of AD, the severity of eczema decreased during the 18-month treatment period from a mean of 37.7 to 20.3 for placebo and from 38.3 to 20.6 for cetirizine (Fig. 1b). The decreases during the study of the global SCORAD index, as well as of the subjective symptom score, the extent score, and the intensity score, were statistically significant in both groups ($p < 0.001$). Statistical analysis according to repeated-measures analysis of variance showed

Table 3. Duration of the use of topical and systemic medications for the treatment of atopic dermatitis during the 18-month study period

Treatment	Placebo (n=397)			Mean*	Cetirizine (n=398)		p-value†
	Mean*	Median	Inter-quartile		Median	Inter-quartile	
Topical medications							
Emollients	58.6	77.7	(2.1, 100)	59.5	81.5	(25, 100)	0.894
NSAI creams	5.9	0	(0, 0)	7.3	0	(0, 0)	0.828
Tar	7.7	0	(0, 0)	7.4	0	(0, 0)	0.971
Antibiotics/antiseptics	6.2	0	(0, 0.18)	4.5	0	(0, 0)	0.146
Local steroids: class I	20.5	0	(0, 30.6)	22.2	0	(0, 34.4)	0.801
Local steroids: classes II, III, IV	25.2	2.4	(0, 45.9)	18.8	0.95	(0.21, 0.95)	0.067
Systemic medications							
Oral H ₁ -antihistaminics	4.4	0	(0, 0)	3.4	0	(2.2–4.7)	0.035
Oral antibiotics	0.16	0	(0, 0)	0.13	0	(0.06–0.19)	0.450

*Mean, median, and inter-quartile range of the percentage of days of each medication.

†Mann-Whitney test.

The percentages are shown of days of use of each medication in the placebo group (n=397) and in the cetirizine group (n=398).

Table 4. The use of topical corticosteroids and local antibiotics and antiseptics for the treatment of atopic dermatitis (AD) in patients with more severe AD (SCORAD ≥ 25 points) at baseline and in patients sensitized to aeroallergens at baseline

Treatment	Placebo	Inter-quartile	Cetirizine	Inter-quartile	p-value†‡
AD with SCORAD ≥ 25 :	n=175		n=172		
Ever used [no of patients (%)]					
Steroids class I	76 (43.4)		81 (47.1)		0.493†
Steroids class II, III, IV	127 (72.6)		109 (63.4)		0.066†
Local antibiotics and antiseptics	64 (36.6)		45 (26.2)		0.037†
Percentage of days* mean (median)					
Steroids class I	23.1 (0)	(0, 37.6)	28.1 (0)	(0, 64.4)	0.366‡
Steroids class II, III, IV	35.1 (20.2)	(0, 69.8)	25.8 (6.2)	(0, 40.6)	0.014‡
Local antibiotics and antiseptics	8.8 (0)	(0, 3.3)	7.2 (0)	(0, 0.5)	0.055‡
AD with sensitization to aeroallergens:	n=82		n=76		
Ever used [no of patients (%)]					
Steroids class I	35 (42.7)		26 (34.2)		0.274†
Steroids class II, III, IV	49 (59.8)		40 (52.6)		0.367†
Local antibiotics and antiseptics	32 (39.0)		17 (22.4)		0.024†
Percentage of days* mean (median)					
Steroids class I	18.8 (0)	(0, 20.1)	19.8 (0)	(0, 29.4)	0.477‡
Steroids class II, III, IV	31.9 (5.0)	(0, 68.5)	19.4 (0)	(0, 26.5)	0.096‡
Local antibiotics and antiseptics	8.6 (0)	(0, 3.5)	5.4 (0)	(0, 0)	0.038‡

*Mean, median, and inter-quartile range of the percentage of days of each medication.

†Chi-square test.

‡Mann-Whitney test.

The percentages are shown of patients using topical steroids or local antibiotics and antiseptics at least once during the 18-month study period as well as the duration of the use of topical steroids and local antibiotics and antiseptics (expressed as percentages of days) during the same 18-month study period. The number of patients (%), mean and median values, and inter-quartile ranges, are shown.

that there were no statistically significant treatment effects and no treatment–time interaction. Patients with elevated IgE aeroallergens at baseline also showed a decrease of the average SCORAD index during the study period (Fig. 1c): from 30.3 to 22.3 in the placebo patients and from 32.6 to 18.8 in the cetirizine patients (from baseline to the last visit).

During the study period there were no significant differences in the occurrence of adverse events. The only exception was the number of patients who developed urticaria, which was significantly lower in the cetirizine group than in the placebo group (placebo group: 16.2%; cetirizine group: 5.8%; $p < 0.001$, chi-square test) (19).

There were no recommendations or restrictions for the treatment of AD during the 18-month study period. The concomitant use of H₁-antihistamines was discouraged, but not restricted. Interestingly, additional oral H₁-antihistamines were used for the treatment of AD by a greater number of patients in the placebo group (24.9%) than in the cetirizine group (18.6%; $p = 0.03$, chi-square test) (19).

The topical and systemic treatment of AD is difficult and depends on the individual disease expression. The number of patients using different treatments did not differ significantly between the placebo and the cetirizine groups (see Table 2). It has to be considered, however, that

the percentage of patients in whom the different treatments were used over an observation period of 18 months was too small for any differences to be evident. More detailed information about the duration and the amount of treatment would be preferable.

Therefore, we also calculated the percentage of days on which these different treatments were used. The mean, median and inter-quartile ranges of the percentage of days of use of several treatments are shown in Table 3. Emollients were used for more than 50% of the days for the treatment of AD. Non-steroidal anti-inflammatory (NSAI) creams, topical treatment with tar, and treatment with antibiotics or antiseptics, respectively, were (on average) applied over $<10\%$ of the days. Mild, local steroids were used for 21% (mean) of the days in the placebo group and for 22% (mean) of the days in the cetirizine group. However, moderate-to-strong topical steroids (class II to IV) were more frequently used in the placebo group than in the cetirizine group: mean 25.2% (median 2.4%) of the days vs. 18.8% (median 0.95%); $p = 0.067$, Mann-Whitney test.

The percentage of days when systemic medications, other than oral antihistamines, were used did not differ significantly between the cetirizine and placebo groups.

The corticosteroid-sparing effect was statistically significant in the sub-group of infants with

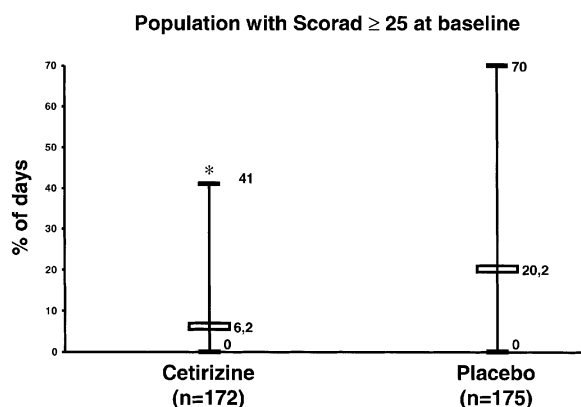


Fig. 2. Duration of the use of topical steroids of classes II, III, and IV in patients with more severe AD at baseline (SCORAD index at baseline ≥ 25). The percentage of days (median and inter-quartile range) of the use of each medication (Mann-Whitney test, $p = 0.014$) are shown.

a SCORAD index of ≥ 25 points at baseline [Fig. 2 and Table 4; 35.1% of days in the placebo group (median 20.2), compared to 25.8% (median 6.2) in the cetirizine group, $p = 0.014$, Mann-Whitney test]. Additionally, topical antibiotics and antiseptics were used by significantly fewer patients and over a shorter period in the cetirizine group compared to the placebo group.

In the sub-group of infants sensitized against aeroallergens (grass pollen and/or house dust mite), the results of medication use were similar to those in the intention-to-treat (ITT) population (Table 4).

Discussion

This is the first study investigating the long-term efficiency of cetirizine on asthma and AD in this specific population. It has been demonstrated that early treatment with cetirizine of infants with AD who are sensitized to grass pollen or house dust mite (raised specific IgE antibody levels ≥ 0.35 kUA/l, e.g. 20% of the study population) reduced by 50% the number of children developing asthma (14). In all infants with AD, however, the natural course of the disease and the treatment were probably influenced by treatment with cetirizine. Fewer children developed urticaria (19) and the need for the use of moderate-to-potent topical corticosteroids could be reduced in the cetirizine group compared to the placebo group. This so-called 'corticosteroid-sparing effect' was statistically significant ($p = 0.014$) in the patients with AD of greater severity (SCORAD index at baseline ≥ 25 points) and was also observed in those patients sensitized to grass pollen or house dust mite ($p = 0.096$).

The severity of AD (as measured by the SCORAD index) decreased (on average) from baseline to the end of the treatment period, 18 months later. This decrease was also observed in the patients with AD of greater severity (SCORAD index at baseline ≥ 25 points) and in those patients sensitized to grass pollen or house dust mite.

In this study, however, the additional use of antihistamines was discouraged, but not restricted. In the placebo group a significantly greater number of patients used oral antihistamines for the treatment of AD compared with the cetirizine group (19). Therefore, we believe that the positive effects of cetirizine on AD could have been even stronger if the use of additional antihistamines in the treatment of AD had been restricted. The fact that antihistamines were used by a greater number of patients in the placebo group also demonstrated that it was often impossible to manage AD over an 18-month period without using antihistamines. This might be an additional indirect hint for the efficacy of antihistamines together with topical treatments in the management of AD.

Cetirizine is approved for the treatment of allergic diseases in children and adults, such as seasonal (20,21) and perennial rhinitis (22,23), as well as chronic urticaria (24,25). In our study the occurrence of urticaria in children was significantly lower in the cetirizine-treated patients (5.8% of patients with at least one episode) compared to the placebo group (16.1%, $p < 0.001$, chi-square test) (19).

In AD, antihistamines are used to stop the itch-scratch cycle, which damages the epidermal barrier leading to increased water loss, enhancing the effect of environmental factors and allergens, and causing flare up and aggravation of skin symptoms. Therefore, one of the most important principles of the treatment of AD is the management of itching. Some studies support the view that antihistamines are not useful in the management of AD and fail to reduce pruritus (26). Most studies on the use of antihistamines in AD are tenuous, do not fulfil essential design criteria for clinical evaluation, and are based on small study populations.

There are a lack of well-designed randomized double-blind studies on the efficacy of cetirizine in patients with AD. The study of La Rosa et al. (27) is based on a total of only 22 patients with AD and a short treatment period of 8 weeks. The results of this preliminary small study suggest effects of cetirizine on pruritus and other cutaneous symptoms in children with AD without noticeable side-effects. Hannuksela et al.

(28) examined 178 adults with AD in a double-blind, parallel, randomized, placebo-controlled study of cetirizine given in three different doses of 10, 20, and 40 mg, daily for 4 weeks. Local therapy with emollients and 1% hydrocortisone was performed in an identical manner in all four groups. Of the 178 case report forms collected, 51 were, however, excluded from statistical analysis of efficacy. The results of the study showed that the concomitant use of cetirizine, in patients suffering from AD and regularly treated with local therapy, improved the disease (erythema, lichenification, total symptom score, area involved, final assessment and pruritus) in a dose-related manner. The incidence of somnolence (sedation) was also dose related. The authors found that the improvement in pruritus was linked to sedation but, conversely, the improvement of skin lesions (which were also dose related) did not differ between the sub-group of patients presenting sedation and those who did not. The authors concluded that sedation is less important in controlling skin lesions and that cetirizine might have other properties responsible for skin-lesion healing. They concluded that AD could be treated with an H₁-blocker such as cetirizine. Some somnolence, when present at higher dose, may help to reduce pruritus but has no effect in controlling skin lesions.

It has been shown that, *in vivo*, cetirizine inhibits eosinophil migration (29) and might have a regulatory effect on adhesion molecule expression (11,12). The corticosteroid-sparing effect observed in our study could be caused by the anti-inflammatory properties of cetirizine. In ETAC, the evaluation of pruritus was incorporated in the SCORAD scale.

In our study, cetirizine was given at a relatively high dose (0.25 mg/kg twice daily) over 18 months. There were no clinically relevant differences between the cetirizine- and placebo-treated groups for neurologic or cardiovascular symptoms (15). The safety of cetirizine has been confirmed in this clinical trial, the longest prospective safety study of any H₁-antagonist ever conducted.

This study was not designed specifically to study efficacy for AD. A study design with AD as the primary end-point should include a more uniform and restricted concomitant treatment regimen and further specific outcome parameters for AD. In the ETAC study a wide variety of additional topical and systemic treatment of AD was employed. Additionally, it has to be considered that SCORAD is a cross-sectional measure and therefore weak in a

long-term study if not performed at short time intervals.

In summary, additionally to the prevention of asthma in a specific sub-group of children with AD, this study might be taken to support the general use of cetirizine in addition to other medications in the treatment of AD. However, well-designed, randomized clinical trials with the primary end-point of AD are required to confirm the effectiveness of cetirizine in the management of AD.

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