

Prevention of acute urticaria in young children with atopic dermatitis

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Background: There are no published prospective, randomized, double-blind, placebo-controlled studies of urticaria prevention in children.

Objective: Our objective was to study the effect of long-term treatment with the H₁-receptor antagonist cetirizine in the prevention of urticaria in young children with atopic dermatitis.

Methods: In the prospective, double-blind, parallel-group Early Treatment of the Atopic Child study, 817 children with atopic dermatitis who were 12 to 24 months of age at study entry were randomized to receive either cetirizine, 0.25 mg/kg, or matching placebo twice daily for 18 months and to be followed up for an additional 6 months, during which time the study medication code remained unbroken. During both these double-blind phases of the study, for a total of 24 months, caregivers prospectively recorded all symptoms and events, including hives, in a diary on a weekly basis when the child was well and on a daily basis when a symptom or event was observed. The diaries were reviewed and validated with the investigators at each regularly scheduled study visit.

Results: Acute urticaria occurred in 16.2% of the placebo-treated children and in 5.8% of the children treated with cetirizine ($P < .001$). The protective effect of cetirizine disappeared when treatment was stopped. In the study population as a whole, urticaria episodes were most commonly associated with intercurrent infection or with food ingestion or direct skin contact.

Conclusion: Acute urticaria is common in toddlers with atopic dermatitis and can be prevented with cetirizine in this high-risk population. (*J Allergy Clin Immunol* 2001;107:703-6.)

Key words: Urticaria, hives, atopic dermatitis, cetirizine, antihistamine, H₁-receptor antagonist, infant, child, prevention

Recommendations for prevention and treatment of urticaria in infants and children¹⁻⁷ are based on extrapolation from evidence obtained in prospective, randomized, double-blind, placebo-controlled clinical trials in adults and on clinical experience in the pediatric population. Most of the retrospective,^{8,9} cross-sectional,¹⁰⁻¹⁴ or prospective¹⁵⁻¹⁷ pediatric studies that have been published are concerned primarily with the cause of urticaria. Many of these studies included adolescents and even adults in addition to infants and children.^{9,10,13-16}

Abbreviation used

ETAC: Early Treatment of the Atopic Child

Although H₁-receptor antagonist use in children with urticaria is described in one cross-sectional study¹¹ and mentioned in one prospective study,¹⁷ there are no published double-blind, placebo-controlled, clinical trials of H₁-antagonists in this population.

A unique opportunity to investigate the potential role of an H₁-receptor antagonist (antihistamine) in urticaria prevention in young children arose during the Early Treatment of the Atopic Child (ETAC) study conducted in 12 European countries and in Canada from 1994 to 1997. In this study 817 12- to 24-month-old children with atopic dermatitis and a family history of allergic disorders were randomized to receive either cetirizine or placebo for 18 months and were followed up in a double-blind manner for an additional 6 months after discontinuation of study medication.

The primary purpose of the ETAC study was to ascertain whether cetirizine treatment would prevent or delay the onset of asthma in these high-risk children. Some outcomes of the study, including a detailed description of the cohort,^{18,19} asthma prevention,²⁰ topical glucocorticoid-sparing effect in atopic dermatitis,²¹ and safety,²²⁻²⁴ have been published previously. Here we describe the effect of cetirizine in prevention of acute urticaria in this population.

METHODS

The study protocol was approved by the institutional review board in each of the participating centers. The children were enrolled after informed consent was obtained from their parents or guardians. The inclusion and exclusion criteria for the ETAC study and the methods of monitoring for efficacy and safety have been described in detail in previous publications.^{20,23} Briefly, the study had a prospective, double-blind, parallel-group, placebo-controlled design. Eight hundred seventeen children with atopic dermatitis but no asthma or other systemic disorder, who were 12 to 24 months old at study entry, and who had at least one allergic parent or sibling were randomized. Of these, 399 actually received cetirizine treatment and 396 received placebo treatment. The cetirizine dose of 0.25 mg/kg twice daily or placebo solution that was similar in appearance was administered as drops with breakfast and with the evening meal every day for 18 months. After treatment with cetirizine or placebo was discontinued, the study continued in a double-blind manner for an additional 6 months.

Throughout the study, the child's primary caregiver used a diary card to record all symptoms, events, and medications administered on a weekly basis when the child was well and a daily basis when the child was having symptoms. At 9 regularly scheduled visits (ie,

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*The members of the ETAC Study Group are listed in the Appendix.

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	Treatment								Follow-up
Visit	1	2	3	4	5	6	7	8	9
Month	0	1	3	6	9	12	15	18	24
Cetirizine Group	411*	398	380	374	368	363	360	356	352
Placebo Group	406*	394	385	377	365	356	351	347	343

FIG 1. Attrition of the study population during 18 months of active treatment and 6 months of follow-up is shown. Both phases of the study were conducted in a double-blind manner. Asterisks refer to randomized children.

TABLE I. Frequency of children with urticaria: Analysis by sex

	Placebo	Cetirizine
During 18 mo treatment		
Girls	27 (18.1%)	6 (3.9%)
Boys	37 (14.9%)	17 (6.9%)
During 6 mo follow-up*		
Girls	9 (6.6%)	4 (3.0%)
Boys	9 (4.3%)	8 (3.7%)

*The data shown for the follow-up period represent the period after discontinuation of the study medication (ie, "ex-cetirizine" and "ex-placebo" groups).

TABLE II. Acute urticaria: Associated factors by history

Infection: 54.5% (upper respiratory or gastrointestinal tract symptoms, fever)
Food allergen ingestion or contact: 24.6% (egg, peanut, milk, fish, meat [ham, turkey], kiwi, tomato, spinach, raspberry, strawberry, chocolate)
Other allergen inhalation or contact: 6.5% (grass pollen, dog, horse, cat, rabbit, hay)
Medications: 3.6% (penicillin, amoxicillin)
Not sure or unknown: 10.8%

before treatment with cetirizine or placebo; at 1, 3, 6, 9, 12, 15, and 18 months during treatment; and at 24 months (6 months after discontinuation of the study treatment), the information recorded in the diary cards was reviewed and validated by the investigator and entered on the case record form. Before data analysis, the description of the symptom or event was transcribed verbatim from the case record forms and classified according to World Health Organization terminology. Symptoms or events with different World Health Organization–preferred terms or different dates of onset were counted as different events. A symptom or event was counted as urticaria when typical hives or areas of skin swelling, redness, and itching, distinctly different from the child's usual inflammatory skin lesions of atopic dermatitis, were reported. The urticaria was considered to be associated with infection if sore throat, pharyngitis, tonsillitis, "cold," upper respiratory tract infection, ear infection, vomiting, diarrhea, gastroenteritis, fever, "flu," or "virus" were reported concurrently with the hives or within the time frame of 7 days before or 7 days after the hives appeared.

In the cetirizine- and placebo-treatment groups, the frequency of children with urticaria was compared using the Fisher exact test. The percentage of days of use of class II, III, and IV topical glucocorticoids was compared using the Mann-Whitney test. Administration of medications in addition to study medication was compared

using the χ^2 test. Statistical analyses were performed using two-tailed tests at the 5% level of significance.

RESULTS

There was a low drop-out rate during the 18-month double-blind treatment phase of the study and during the 6-month double-blind follow-up phase (Fig 1). During the 18-month treatment phase, there was a high compliance rate with study medication in both the cetirizine- and placebo-treated children.^{20,23} In the cetirizine-treated children, the total daily dose ranged from 5 to 11 mg.

During the 18-month treatment phase, in the study population as a whole, 87 children experienced 138 episodes of urticaria. Sixty-six children had one episode, 10 had 2 episodes, and 11 had from 3 to 10 episodes. Urticaria occurred with similar frequency in boys and girls (Table I); boys comprised 62% and girls 38% of the study population as a whole. The mean age at onset of the first episode of urticaria was 25 ± 7 months (range, 13–40 months). Urticaria episodes were commonly associated with intercurrent infection or with food ingestion or direct skin contact (Table II).

Urticaria occurred in children with mild, moderate, and severe atopic dermatitis, as assessed at the regularly scheduled visits by using the SCORAD, an index for scoring atopic dermatitis¹⁸; the presence or absence of urticaria did not correlate with the severity of the atopic dermatitis. During the 18-month treatment phase, cetirizine had a significant steroid-sparing effect ($P = .014$), as reflected in fewer days on which class II, III, and IV (moderately potent or potent) topical glucocorticoids were applied to the skin in children with the most severe atopic dermatitis (SCORAD >25 at baseline).²¹

During the 18-month treatment phase, only 23 (5.8%) of the 399 children treated with cetirizine had one or more episodes of urticaria in contrast to 64 (16.2%) of the 396 children treated with placebo ($P < .001$; Fig 2, A). Also, the children treated with cetirizine had fewer episodes of urticaria per child (Fig 2, B). During the 6-month follow-up phase, there was no difference with regard to the number of episodes of urticaria in the children previously treated with cetirizine and those previously treated with placebo (Fig 2, C).

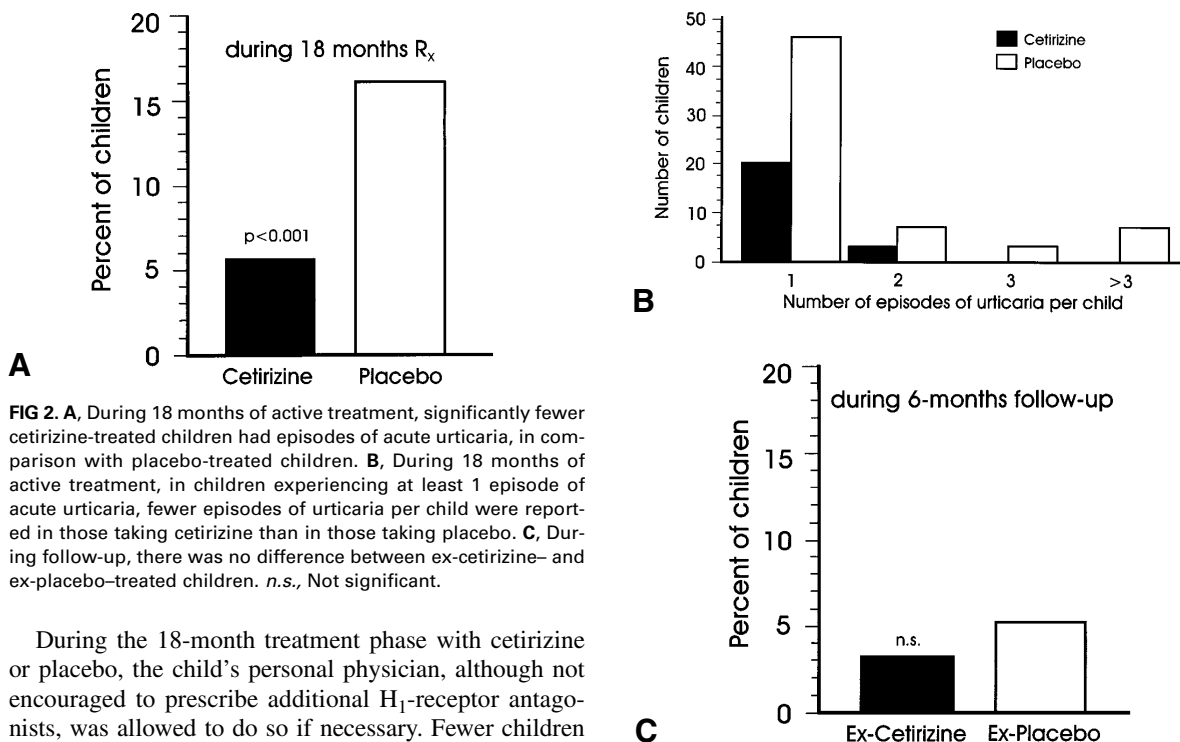


FIG 2. **A**, During 18 months of active treatment, significantly fewer cetirizine-treated children had episodes of acute urticaria, in comparison with placebo-treated children. **B**, During 18 months of active treatment, in children experiencing at least 1 episode of acute urticaria, fewer episodes of urticaria per child were reported in those taking cetirizine than in those taking placebo. **C**, During follow-up, there was no difference between ex-cetirizine- and ex-placebo-treated children. *n.s.*, Not significant.

During the 18-month treatment phase with cetirizine or placebo, the child's personal physician, although not encouraged to prescribe additional H_1 -receptor antagonists, was allowed to do so if necessary. Fewer children treated with cetirizine (138/399 [34.6%]) received additional oral prescription or nonprescription H_1 -antagonists in comparison with those treated with placebo (164/396 [41.4%], $P = .047$).

DISCUSSION

Here we report, for the first time in a long-term, prospective, randomized, double-blind, controlled study in over 800 young children with atopic dermatitis, that acute urticaria was common, occurring in 16.2% of placebo-treated children. The prevalence of urticaria was only 5.8% ($P < .001$) in children treated with cetirizine on a regular basis; however, the significant protective effect of the H_1 -receptor antagonist was lost when active treatment was discontinued. In the placebo/"ex-placebo" group, although the percentage of children who developed urticaria appeared to decline from 16.2% during 18 months of placebo treatment to 5.3% during 6 months of follow-up, these numbers cannot be compared directly because the observation periods differed considerably in length.

A relatively high cetirizine dose, approximately twice that recommended worldwide for use in children age 2 to 6 years, was administered in this study. Despite this, as reported in detail in a previous publication,²³ there were no statistically significant or clinically relevant differences between the cetirizine and placebo treatment groups with regard to safety outcomes. This was documented by scrutiny of all symptoms and events, including those in the neurologic and cardiovascular systems; regular physical examinations, including height and weight measurements and behavior and development assessments; and regular monitoring of laboratory tests,

including electrocardiograms, complete blood counts, blood chemistry tests, and urine analyses.

The rationale for twice daily dosing was that in very young children cetirizine has a shorter terminal elimination half-life and a shorter duration of action,²⁵ as assessed by suppression of the histamine-induced wheal-and-flare response in the skin, than it does in older children and adults. Cetirizine achieves high concentrations in the skin,²⁶ and its preventative effect in urticaria is likely due primarily to histamine blockade at cutaneous H_1 -receptors.

In adults with chronic urticaria, clinical tolerance to histamine is reduced, and histamine concentrations are elevated in urticarial lesions in comparison with the surrounding uninvolved skin. Histamine, acting through its H_1 - and H_2 -receptors on the postcapillary venules in the skin, can mediate all the pathologic features of urticaria: vasodilation, increased vascular permeability, and wheals.²⁷ Acting through H_1 -receptors on small, unmyelinated, extensively branching, slow-conducting C fibers in the skin, it leads to pruritus and erythema.²⁸ In the treatment of urticaria, as in other allergic disorders, H_1 -antagonists are most effective when used prophylactically on a regular basis before symptoms occur, by binding to histamine receptors and preventing histamine from binding.

Current recommendations for the prevention and treatment of urticaria in children¹⁻⁷ are based on information obtained from clinical trials in adults, in whom H_1 -antagonists significantly reduce the number, size, duration, and itching of wheals,²⁹ and on decades of H_1 -antagonist use in children. In the ETAC study we provide evidence that regular treatment with the H_1 -antagonist cetirizine effectively reduces acute episodes of urticaria in young

children with atopic dermatitis. Loss of protection after discontinuation of cetirizine provides additional evidence of H₁-antagonist effectiveness in preventing urticaria in this high-risk population.

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REFERENCES

- Greaves MW. Chronic urticaria in childhood. *Allergy* 2000;55:309-20.
- Kwong KY, Maalouf N, Jones CA. Urticaria and angioedema: pathophysiology, diagnosis, and treatment. *Pediatr Ann* 1998;27:719-24.
- Twarog FJ. Urticaria in childhood: pathogenesis and management. *Pediatr Clin North Am* 1983;30:887-98.
- Casale TB. Urticaria and angioedema. In: McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB, eds. *Oski's pediatrics. Principles and practice*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 2049-53.
- Hobbs KF, Schocket A. Urticaria and angioedema. In: Bierman CW, Pearlman DS, Shapiro GG, Busse WW, eds. *Allergy, asthma, and immunology from infancy to adulthood*. 3rd ed. Philadelphia: W.B. Saunders Company; 1996. p. 643-52.
- Sly M. Urticaria/angioedema (hives). In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson's pediatrics*. 16th ed. Philadelphia: W.B. Saunders Company; 2000. p. 684-5.
- Buckley RH. Urticaria and angioedema. In: Rudolph AR, Hoffmann JIE, Rudolph CD, eds. *Rudolph's pediatrics*. 20th ed. Stamford (CT): Appleton and Lange; 1996. p. 473-4.
- Legrain V, Taïeb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. *Pediatr Dermatol* 1990;7:101-7.
- Ghosh S, Kanwar AJ, Kaur S. Urticaria in children. *Pediatr Dermatol* 1993;10:107-10.
- Jordaan HF, Schneider JW. Papular urticaria: a histopathologic study of 30 patients. *Am J Dermatopathol* 1997;19:119-26.
- Tuchinda M, Srimaruta N, Habanananda S. Urticaria in Thai children. *Asian Pac J Allergy Immunol* 1986;4:41-5.
- Guillet MH, Guillet G. L'urticaire alimentaire de l'enfant: revue de 51 observations. *Allerg Immunol (Paris)* 1993;25:333-8.
- Sakurai M, Oba M, Matsumoto K, Tokura Y, Furukawa F, Takigawa M. Acute infectious urticaria: clinical and laboratory analysis in nineteen patients. *J Dermatol* 2000;27:87-93.
- Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. *Br J Dermatol* 1998;138:635-8.
- Volonakis M, Katsarou-Katsari A, Stratigos J. Etiologic factors in childhood chronic urticaria. *Ann Allergy* 1992;69:61-5.
- Ehlers I, Niggemann B, Binder C, Zuberbier T. Role of nonallergic hypersensitivity reactions in children with chronic urticaria. *Allergy* 1998;53:1074-7.
- Mortureux P, Léauté-Labrèze C, Legrain-Lifermann V, Lamireau T, Sarlangue J, Taïeb A. Acute urticaria in infancy and early childhood. *Arch Dermatol* 1998;134:319-23.
- Oranje AP, Stalder J-F, Taïb A, Tasset C, de Longueville M, on behalf of the ETAC Study Group. Scoring of atopic dermatitis by SCORAD using a training atlas by investigators from different disciplines. *Pediatr Allergy Immunol* 1997;8:28-34.
- Warner JO, for the ETAC Study Group. Determinants of total and specific IgE in infants with atopic dermatitis. *Pediatr Allergy Immunol* 1997;8:177-84.
- Wahn U, for the ETAC Study Group. 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. *Pediatr Allergy Immunol* 1998;9:116-24.
- Diepgen TL. Impact of cetirizine on atopic dermatitis. *J Eur Acad Dermatol Venerol* 1999;12:S133.
- de Longueville M, Deruyter B, RR, QT, and QTc in 799 infants aged 1-2 years. *J Allergy Clin Immunol* 1998;101:S198.
- Simons FER, on behalf of the ETAC Study Group. Prospective, long-term safety evaluation of the H₁-receptor antagonist cetirizine in very young children with atopic dermatitis. *J Allergy Clin Immunol* 1999;104:433-40.
- Ridout SM, Tariq SM. Cetirizine overdose in a young child. *J Allergy Clin Immunol* 1997;99:860-1.
- Spicak V, Dab I, Hulhoven R, Desager J-P, Klanova M, de Longueville M, et al. Pharmacokinetics and pharmacodynamics of cetirizine in infants and toddlers. *Clin Pharmacol Ther* 1997;61:325-30.
- Simons FER, Murray HE, Simons KJ. Quantitation of H₁-receptor antagonists in skin and serum. *J Allergy Clin Immunol* 1995;95:759-64.
- Simons FER, Simons KJ. The pharmacology and use of H₁-receptor antagonist drugs. *N Engl J Med* 1994;330:1663-70.
- Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjörk HE. Specific C-receptors for itch in human skin. *J Neurosci* 1997;17:8003-8.
- Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. *Ann Pharmacother* 1996;30:1075-9.

APPENDIX 1: ETAC STUDY GROUP

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