

LONG-TERM CETIRIZINE TREATMENT MAY REDUCE NEW SENSITISATIONS IN ALLERGIC CHILDREN : A PILOT STUDY

G. Ciprandi M.D. ⁽¹⁾, F. Frati M.D. ⁽²⁾, F. Marcucci M.D. ⁽²⁾, L. Sensi MD ⁽²⁾,
M. Milanese ⁽¹⁾, M.-A. Tosca M.D. ⁽²⁾

Summary

Experimental data demonstrate that mite allergy is characterized by persistent chronic inflammation. This suggests that long-term continuous treatment may be included in the global strategy of allergy management as recently reported. Moreover, most of allergic subjects show polysensitisation.

We conducted a study to investigate whether a long-term cetirizine treatment may reduce the occurrence of new sensitisations in children with mite allergy.

This study was initially double-blind, randomized, and placebo-controlled, with two parallel groups of 10 children with mite allergy receiving either cetirizine or placebo daily. All children could assume cetirizine as rescue medication (i.e. symptomatic treatment). After six months, parents of continuously-treated children decided to continue the treatment for 3 years. Other subjects continued to assume cetirizine on symptomatic basis.

All children were prospectively followed for other 3 years. Outcome measure was skin prick test, yearly performed. Cetirizine-continuously-treated group showed a significant lower incidence of new sensitisations ($p = 0.002$).

In conclusion, cetirizine administered daily for prolonged periods (i.e. 3 years) may decrease the development of new sensitisations in monosensitised children, showing a potential effect of tertiary prevention of allergy.

Key-words : Cetirizine - Long-term treatment - Polysensitisation - Tertiary prevention

INTRODUCTION

Allergic rhinitis and asthma are the most common IgE-mediated diseases and their prevalence is still increasing. Moreover, an association between asthma and allergic rhinitis is frequently observed, as well as the natural history of allergic patients is commonly characterized by the phenomenon of polysensitisation (1).

The allergic reaction is not a short-lived phenomenon, but rather a dynamic process characterised by an inflammatory response (2). If exposure to the causal allergen persists, allergic inflammation is invariably detected in sensitised individuals, even when the patient is asymptomatic (the so-called "minimal persistent inflammation" - MPI) (3).

Mite allergy is associated with chronic inflammation, and clinical relapses are frequently due to such other environmental factors as viral infections. This would

explain the association between respiratory viral infections and asthma exacerbations in allergic children (4).

Taken together, these data suggest that long-term, regularly administered pharmacologic treatment might be more effective than "on-demand" symptomatic treatment.

Cetirizine is a highly selective antihistamine that exerts antiallergic effects (5). Indeed, it prevents the changes induced by allergen-specific challenge and reduces eosinophil and neutrophil infiltration at the site of the allergic reaction (6). Furthermore, cetirizine decreases ICAM-1 expression on nasal epithelial cells, thus reducing the susceptibility of epithelial cells to leukocyte infiltration, and also controls MPI (7).

Patients with seasonal allergic rhinitis responded better to continuous administration of cetirizine than to symptomatic treatment (8). More recently, we demonstrated that long-term cetirizine treatment reduced allergic symptoms and drug prescription in children with

⁽¹⁾ Allergy-ENT Unit, Head Neck Dpt. - San Martino Hospital - Genoa (Italy).

⁽²⁾ Department of Obstetric - Gynaecologic and Pediatric Sciences University of Perugia (Italy).

mite allergy (9). Moreover, the ETAC study indicated that continuous antihistaminic treatment exerted a prophylactic effect on the asthma onset in atopic children (10).

These findings prompted us to investigate whether continuous long-term treatment with cetirizine might reduce the onset of new sensitizations in monosensitized children with respiratory allergy.

MATERIALS AND METHODS

STUDY DESIGN

This was initially a randomized, double-blind, placebo-controlled study with two parallel groups of 10 children, randomly coded prior to the study, receiving either daily cetirizine or placebo for six months. Cetirizine (oral drops) was prescribed at the recommended dosage (i.e. 5 mg/day). The placebo was indistinguishable in appearance and taste from the active product. All patients were allowed to assume cetirizine (5 mg/day) as symptomatic drug when needed. Thus, placebo-group could be considered as symptomatically treated.

This study aimed to evaluate pharmacoeconomic issues and has been already published (9). The study was approved by the Ethics Committee of the Department of Internal Medicine. Parental consent was obtained for all children. The study started in October 1996 and ended in April 1997, at which time the double-blind key was revealed. Then, parents of continuously-treated children spontaneously decided to continue treatment for further 30 months, since perceived good results with this treatment. Other children continued a symptomatic use of cetirizine for the same period.

All children were followed for the successive 3 years, during this period all of them assumed cetirizine on demand.

PATIENTS

Twenty patients (15 males and 5 females), aged between 3 and 10 years (mean age 6.5 years), were selected from an outpatient population, and enrolled in the study. All patients showed isolated sensitisation to house dust mite, assessed by skin testing (wheal > 3 mm, +++ or more) and RAST (class III or higher). The patients suffered from perennial rhinitis and/or from mild intermittent asthma.

Asthma was clinically diagnosed according to GINA criteria (11) and, when possible, spirometry was per-

formed in children old enough to collaborate. No child suffered from anatomical alterations of the upper airways, immunologic deficiencies or major systemic diseases (diabetes, anaemia, cystic fibrosis, inherited metabolic disorders). No child had a history of cardiac disease and/or arrhythmia.

The following precautions were recommended for environmental care: allergen-proof covers for mattresses and pillows, and no carpets, curtains or pets in the bedroom. Beds and furniture were vacuumed carefully once or twice a week, humidity in the house was kept as low as possible and no smoking was permitted in the house. Acaricides were not recommended.

■ **Outcome of the study :** the occurrence of new sensitisations was considered the objective of the study. New sensitisations were appropriately recorded in an apposite form.

■ **Skin prick test** was performed according to standardised and validated criteria (1). Children withheld antihistaminic medication for four days prior to skin prick testing. A standard panel of allergens was used : house dust mites (*Dermatophagoides pteronyssinus* and *farinae*), *Graminaceae* mix, *Parietaria judaica*, olive tree, birch, hazelnut, cat dander, dog dander and *Aspergillus fumigatus*, using commercial extracts (DHS-Bayer, Milan, Italy) in addition to a positive (histamine) and negative (diluent) control. Results were read after 15 min, a positive reaction being defined as a weal diameter of 3 mm greater than negative control.

■ **Assessment of newly developed sensitisation :** in 1996 all children were just monosensitized to *Dermatophagoides* as determined by skin prick test and RAST. Yearly children underwent to skin prick test by using the same panel of allergens.

■ **Statistical analysis :** it was performed using χ^2 square test. Differences were considered significant if p values were < 0.05.

RESULTS

All of the 20 patients completed the study. No significant side effects were observed. The baseline demographic data were similar in the two groups.

All of the children were sensitized to *Dermatophagoides* only at enrolment in 1996.

The number of monosensitized children is reported in detail in figure 1.

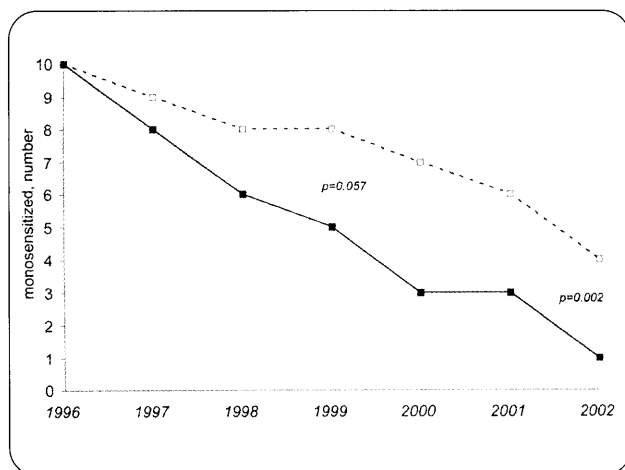


Figure 1.

■ **Continuously-treated children :** at the end of continuous treatment (i.e. after 3 years), only 2 children showed polysensitisation, with a trend of difference in comparison with the other group ($p = 0.057$). At the end of the observational period (i.e. after 6 years), 7 children were polysensitised, particularly 3 children were sensitised to only two allergenes, whereas 4 children were sensitised to more than 2 allergens, with a significant difference in comparison with the other group ($p = 0.002$).

■ **Symptomatically-treated children :** after 3 years, 5 children showed polysensitisation. After 6 years, 9 children showed new sensitisations. One child alone showed polysensitisation to two allergens only, whereas 8 children had polysensitisation to more allergens.

DISCUSSION

It is generally agreed that an allergic reaction is sustained by an inflammatory response (2, 3). In the light of this assumption, we evidenced that long-term continuous antihistaminic treatment represents a better strategy for allergy management than the widely used "symptomatic" treatment (8, 9, 12).

Cetirizine is a second-generation antihistamine with antiallergic properties (5). It is effective in controlling inflammatory events, including ICAM-1 down-regula-

tion on epithelial cells (6). Moreover, cetirizine reduces the eosinophil infiltration and eosinophilic cationic protein levels in nasal lavage in allergic children (13).

On the other hand, it is well known that allergic children commonly develop polysensitisation, as broadly reported by Silvestri and coll. (14).

Specific immunotherapy has been demonstrated to have the potential to modify the natural history of the allergic disease with regard to the development of polysensitisations and disease progression (15, 16).

The present study shows that continuous long-term treatment with cetirizine may reduce the onset of new sensitisations in children with mite allergy. This finding may be considered the first evidence of a "tertiary prevention" of allergic disorders provided by an antihistamine.

Consequently, the pharmacological therapeutical strategy for allergic rhinitis should be reassessed and targeted to inflammation control, rather than to symptom relief only. This could be achieved by using continuous long-term treatments instead of "on demand" treatment. Cetirizine, which reduces inflammation by affecting the recruitment and activation of inflammatory cells, seems to be suitable for the continuous treatment of allergy. Moreover, cetirizine can exert prophylactic effects in natural history of allergic diseases. In this regard, the ETAC study constitutes a clear evidence of "secondary prevention" of allergic disease (i.e. asthma onset in "at risk" infants) exerted by an antihistamine (10).

The ETAC study provides some lessons, concerning the properties of cetirizine, which may be summarised as follows :

- prevention of asthma in a subgroup of aero-allergen (i.e. grasses and house dust mite) sensitised atopic dermatitis infants ;
- the best safety profile among antihistamines for infants ;
- reduction of high potency topical steroid requirements for atopic dermatitis ;
- reduction of acute urticarial episodes and additional antihistamine requirements ;
- no significant effects on behavioral, cognitive, and psychomotor development in treated infants.

	Parietaria	Graminaceae	Hazelnut	Olive tree	Birch	Cat dander	Aspergillus
Cetirizine	2/7	3/7	2/7	2/7	1/7	1/7	1/7
Placebo	7/9	5/9	1/9	3/9	3/9	1/9	1/9

Table 1 : Distribution of subjects' polysensitization after 6 years from baseline. Data are expressed as number of subjects sensitized to described allergen to total number of polysensitized subjects.

Of course, our study concerns a very little cohort of allergic children. Thus, several studies should be performed on larger patient populations to verify our findings. Further confirms might derive from studies concerning the pre-

vention of allergic progression in children, for example the ongoing EPAC study might be addressed also to this issue.

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