Effect of long-term cetirizine treatment on the cutaneous hypersensitivity reaction in patients with grass pollen allergy

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Abstract. In short-term studies cetirizine effectively reduces the early and late phases of the cutaneous hypersensitivity reaction. The aim of this study was to determine its long-term effects on both the vascular and cellular components of the reaction.

The skin blister technique was used to collect inflammatory cells after intradermal administration of grass pollen antigen to 10 atopic volunteers. They were treated for 3 months with 10 mg cetirizine twice daily. Tests were done at baseline, before, and 7, 30 and 90 days after initiation of treatment. Blister fluid containing cells was collected on microscope slides at 6 and 24 hours. The area of induration was measured at 0.25, 1, 6, 10 and 24 h.

Cetirizine significantly reduced the peripheral blood eosinophil count at 30 and 90 days (75% and 40% reduction respectively); there was no significant change after only one week's therapy. Eosinophil recruitment to and activation in the area of antigen administration were already maximally reduced after 7 days, namely a reduction of 54, 52 and 59% at 10 h, and of 55, 68 and 66% at 24 h, respectively, at 7, 30 and 90 days. The area of induration was significantly reduced after one week of therapy. There was a general tendency towards an increase in the reduction at 30 and 90 days, which reached significance only at the 24 h observation; there was a 24, 51 and 48% reduction from baseline at, respectively, 7, 30 and 90 days.

The data clearly show a progressive reduction of inflammation as well as of cellular events over time. The maximum effect occurred at 30 days, after which no further reduction was detected up to 90 days.

We conclude that this progressive suppression of inflammation is possibly due to the inhibitory effect of cetirizine on the release of cytokines and other mediators of the hypersensitivity reaction.

Key words: Cetirizine; cutaneous hypersensitivity reaction, eosinophil response, grass pollen allergy, blister fluid

In short-term studies, cetirizine, a selective H₁ receptor blocker (Zyrtec® UCB), reduced the early and late phases of the cutaneous hypersensitivity reaction [1–4]. This is not simply due to inhibition of mast cell degranulation, but also to a reduction both in local cell migration, and in reactivity in the area of antigen administration [1–4]. Recognition of these effects has led to the widespread use of cetirizine in various atopic disease states, such as rhinitis, eczema and even asthma [5]. In patients with asthma a clear improvement in pulmonary response (i.e. an increase in FEV₁) and forced vital capacity) and a reduction in the concomitant use of other asthma medications, either for prophylaxis or the symptomatic relief of symptoms, has been demonstrated over time [6–8]. It is possible, therefore, to suggest a progressive reduction in immune reactivity over time.

The aim of the present study was to establish whether the reduction in inflammatory cell recruitment and activation seen during acute experiments with cetirizine became more pronounced over a prolonged treatment period.

Materials and methods

Ten atopic volunteers, 2 female and 8 males, aged 19 to 22 y, were recruited for the study. Strict inclusion criteria were applied and only volunteers allergic to grass pollens, and who gave a history of allergic rhinitis, conjunctivitis or asthma during the pollen season were admitted to the trial. They had taken no medication for at least one month prior to testing, which was done outside the pollen season. All the selected volunteers reacted with at least a 20 mm diameter wheal, followed by a late phase cutaneous hypersensitivity reaction, to intradermally administered antigen (Southern Grass Mix, Bayer Miles), and none showed a reaction to the saline control. The protocol was approved by the Ethical Committee of the University of Pretoria and the volunteers gave written informed consent to it.

In this open study, the volunteers were treated for 3 months with 10 mg cetirizine bd (Zyrtec® UCB, SA). The dose was the same as that used previously in short-term studies, in which it was proven effectively to suppress vascular events and eosinophil recruitment or activity [3–5]. Skin tests and peripheral blood differential counts were done before (baseline) and at 7, 30 and 90 days after initiation of treatment.
**Table 1.** Median percentages (with 95 % confidence interval) of eosinophils (EOS) in the peripheral blood (PB) as well as those accumulated (A) and the percentage vacuolated (V) at the skin test site at the different follow-up periods

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>7 days</th>
<th>30 days</th>
<th>90 days</th>
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<tbody>
<tr>
<td>PB-EOS</td>
<td>2.75 (2.2-3.4)</td>
<td>3.40 (2.2-5.6)</td>
<td>0.70** (0.1-2.1)</td>
<td>1.90** (1.5-2.6)</td>
</tr>
<tr>
<td>EOS-A</td>
<td>24.70 (13.2-17.7)</td>
<td>18.10 (13.2-40.8)</td>
<td>11.0* (5.2-16.6)</td>
<td>9.0* (7.3-17.9)</td>
</tr>
<tr>
<td>EOS-V</td>
<td>23.10 (17.7-33.2)</td>
<td>19.90 (13.9-31.3)</td>
<td>0.0* (0.1-4.5)</td>
<td>0.0* (0.0-7.1)</td>
</tr>
</tbody>
</table>

* Differs significantly from baseline (P < 0.05)
** Differs significantly from baseline and 7 days (P < 0.05)

**Fig. 1.** Median area of the wheal and flare reaction (95 % confidence interval) at the different follow-up periods 15 minutes after antigen administration. Cetirizine significantly reduced the reaction at all follow-up periods. * Significantly less than baseline (P ≤ 0.05); ** Significantly less than placebo and 7 days (P ≤ 0.05)

The skin blister technique was used as a noninvasive in vivo method to study drug effects on inflammatory cell dynamics [9]. Two suction blisters, each of 8 mm diameter, were simultaneously induced on the volar aspect of one forearm, a fresh area on the alternate forearm was also used at random each time. The blisters were induced over approximately 2 h by vacuum suction at a negative pressure of 300 mm Hg [4]. Thereafter, aliquots of 10 PNU/0.05 ml of Southern Grass Mix (containing extracts of Kentucky Blue, Orchard, Redtop, Timothy, Sweet Vernal, Bermuda and Johnson grass varieties), were injected intradermally in the base of each blister. The blisters were left intact and were covered with a small Petri dish for protection until blister fluid was collected at 10 h and 24 h. Microscope slides were made with the blister content, and, after air-drying, they were stained with May-Grünwald-Giemsa solution. A differential cell count was performed in order to determine the percentage of each type of inflammatory cell in a total count of 500 cells. These cells were distinguished according to generally accepted criteria [10].

In order to estimate eosinophil activity, the percentage of vacuolated cells (minimum of three vacuoles in the cytoplasm) were counted, as this is correlated with the physiological function of the cell at the site of antigen administration [4,11,12]. Cell differentiation was done by a co-worker blind to the treatment protocol.

The surface areas of the immediate and late phase skin reactions were evaluated by marking the perimeters of the reactions at 0.25, 1, 6, 10 and 24 h. The boundaries were transferred to transparent plastic film for subsequent measurement by computerised planimetry.

In an attempt to ensure patient compliance, a random blood sample was taken from each of the volunteers 4 h after a morning dose for the measurement of plasma cetirizine [13].

Statistical analysis employed Friedmans two way analysis of variance [14] for multiple comparisons between variables to the different observation periods. With this method changes within each individual and not between them were compared. As it is a test for non-parametric data, the medians and 95 % confidence intervals were used for visual interpretation only and were not used for statistical analysis. Changes were taken to be significant at the 5 % level.

**Results**

**Peripheral blood leucocytes (Table 1)**

All volunteers had normal peripheral white cell counts throughout the trial period. There was no significant change in eosinophil count after only one week of therapy. However, the latter was significantly lower at 30 and 90 days compared to the values at baseline and one week; there was a mean reduction from baseline of 75 % and 40 % and from one week of 80 % and 50 %, respectively, at 30 and 90 days.

**Measurement of wheal and flare response and area of induration of the late-phase reaction**

Cetirizine significantly reduced the wheal and flare reaction from baseline at all observation periods. Although only the flare reaction was significantly reduced after 30 days compared to one week's therapy; there was a tendency for the wheal to be smaller at 30 and 90 days (Fig. 1). The area of induration (at 1, 6, 10 and 24 h) was already significantly reduced after one week of cetirizine therapy, and there was a general tendency towards a further reduction at 30 and 90 days. This latter trend reached significance only at the 24 h observation, with a mean reduction of 24, 51 and 48 % from baseline for the corresponding observation periods of 7, 30 and 90 days. The areas of indu-