I.T.E.M.

Medical Report

for

U.C.B.

Title: A MULTICENTER, DOUBLE-BLIND STUDY OF THE EFFICACY AND SAFETY OF CETIRIZINE 10 MG PER DAY (ONE 5 MG TABLET WITH THE MORNING AND EVENING MEALS) VS PLACEBO, ADMINISTERED FOR 2 WEEKS TO CHILDREN BETWEEN 6 AND 12 YEARS OF AGE, SUFFERING FROM SEASONAL ALLERGIC RHINITIS (PCF90A301)

U.C.B. Study: A166

I.T.E.M. Project: 912

Date: 28/03/91 Author: Dr. B. TISSERAND

/fh
June 1992
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<table>
<thead>
<tr>
<th>NAME OF THE COMPANY:</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAME OF THE FINAL PRODUCT:</td>
<td>ZYRTEC</td>
</tr>
<tr>
<td>NAME OF THE ACTIVE PRINCIPLE:</td>
<td>CETIRIZINE</td>
</tr>
<tr>
<td>TITLE OF THE STUDY:</td>
<td>A multicenter, double-blind study of the efficacy and safety of cetirizine 10 mg per day (one 5 mg tablet with the morning and evening meals) vs placebo, administered for 2 weeks to children between 6 and 12 years of age, suffering from seasonal allergic rhinitis (PCF90A301).</td>
</tr>
<tr>
<td>COORDINATOR:</td>
<td>Doctor M. GROSCLAUDE.</td>
</tr>
<tr>
<td>OBJECT OF THE STUDY:</td>
<td>To test the efficacy of cetirizine at a dose of 10 mg per day, and to complete the data concerning its safety in children between 6 and 12 years of age, suffering from seasonal allergic rhinitis.</td>
</tr>
<tr>
<td>DIAGNOSIS:</td>
<td>Documented to be predominantly seasonal allergic rhinitis (on the basis of history and positive tests).</td>
</tr>
<tr>
<td>PHARMACEUTICAL FORM, ROUTE OF ADMINISTRATION, DOSAGE:</td>
<td>cetirizine 10 mg/day in 2 oral doses (5 mg tablets), placebo in 2 oral doses (identical tablets).</td>
</tr>
<tr>
<td>DURATION OF TREATMENT:</td>
<td>2 weeks.</td>
</tr>
</tbody>
</table>
### CRITERIA OF EVALUATION:
- Daily auto-evaluation scores by the patients:
  - % of days with a score = 0 PDS0
  - % of days with a score ≤ 1 PDS1 (principal criteria)
  - % of days with a score ≤ 2 PDS2
- Scores given by the investigator.
- Global evaluation by the investigator.
- Comparison of adverse events in the 2 groups.
- Comparison of lab tests abnormalities.

### STATISTICAL METHODS:
- The threshold of significance was taken to be: 5% (bilateral tests).
- Scores (auto-evaluation):
  - Cumulated relative frequency distributions of the maximal scores,
  - Comparisons of the medians using Wilcoxon’s rank test.
- Scores attributed by the investigator: Cochran - Mantel - Haenszel test (C.M.H.), based on the ranks and stratified according to the initial score.
- Global evaluation: Mann-Whitney test.
- Adverse events: chi-squared test.

### CONCLUSION:

The object of this phase-III, multicenter (15 centers) double-blind study of cetirizine versus placebo was to confirm the therapeutic efficacy of cetirizine at a dose of 10 mg per day in 2 divided doses, and to complete the data concerning the safety of the product in children between 6 and 12 years of age, suffering from seasonal allergic rhinitis, and treated for 2 weeks.

92 children were included in the pollen season between May and September of 1990; of these, 91 were analyzable, 44 in the cetirizine group, and 47 in the placebo group.

The results, as judged on the principal criterion of judgement retained, namely the percentage of days with a maximal score (whatever the symptom) equal to or less than 1 on daily auto-evaluation by the patients, did not show any significant difference between the 2 treatment groups.
However, there are several arguments in favor of the cetirizine group:

- the percentage of days with a maximal score of 0 (absence of any symptoms) on daily auto-evaluation was 3 times greater in the cetirizine group (5.6 % versus 1.8 %).

- the mean maximal score (as attributed by the investigator) between visits 1 and 3 improved more in the cetirizine group (falling from 2.7 to 1.8) than in the placebo group (falling from 2.8 to 2.2), with a similar change in the mean total score, which improved by 4.9 points in the cetirizine group, versus only 3.6 points in the placebo group.

- the number of dropouts from the study due to inefficacy, although small, was twice as great in the placebo group (14.9 %) than in the cetirizine group (6.8%).

- The onset of further symptoms of the disease being studied was 6 times more frequent in the placebo group (25.5 %) than in the cetirizine group (4.5%).

As regards the adverse events, (any new or unfavorable events), these were twice as frequent in the placebo group (29 events in 21 patients) as in the cetirizine group (13 events in 8 patients). However, if we exclude those events which were considered straightaway to be unrelated to the treatment by the investigator, the incidence if adverse events is comparable in the 2 groups: 9 in 6 patients in the cetirizine group, versus 7 in 6 patients in the placebo group.

The vast majority of these events were minor. There were no cases of somnolence, and no serious adverse events were reported.

The laboratory tests conducted did not show any special abnormalities during treatment.

The global evaluation of the treatment by the investigator was markedly in favor of the cetirizine group (p = 0.002).
1. INTRODUCTION

Cetirizine, a powerful antihistamine belonging to the piperazine family, is already commercially available for the treatment of allergic rhinitis in the adult, where it is administered in a single daily dose of 10 mg (1 to 5).

As the plasma half-life is shorter in children (6.5 h) than in adults (9.5 h) (6), the first studies conducted with this molecule in pediatrics were done using 2 doses per day.

A dose determination study looking for the active dose (7) established that a dose of 2 x 5 mg/d of cetirizine, when given to children between 6 and 12 years of age, for the treatment of seasonal allergic rhinitis, is both effective and well tolerated.

Another study (8) showed that in children between 6 and 12 years of age suffering from seasonal allergic rhinitis, there was no clinically pertinent difference between administering 10 mg/d of cetirizine in a single dose, or in 2 divided doses of 5 mg.

It is therefore necessary to confirm the activity and safety of a daily dose of 10 mg of cetirizine in children.

2. OBJECTIVES

The objectives of this study were:

1) to check the therapeutic effects of a daily dose of 10 mg of cetirizine administered in two doses of one 5 mg tablet each, as compared to placebo,

2) to complete the data on the safety of cetirizine, in children between 6 and 12 years of age, suffering from seasonal allergic rhinitis, treated for 2 weeks.

3. METHODOLOGY

3.1. Design of the study

This was a multicenter, phase III, double-blind study of cetirizine versus placebo, involving two parallel groups of 50 patients, followed-up on an outpatient basis.

The randomisation was conducted at the initial visit, and was balanced, for each center, in blocks of 2 patients.

The treatment period was 2 weeks, the patients receiving one tablet in the morning and one in the evening, of either cetirizine (10 mg/24 h) or placebo. The study was conducted in the pollen season.
3.2. Ethical aspects

- As it was possible to leave the study due to inefficacy after 2 days of properly administered treatment, it was legitimate to use placebo as the reference product.

- The study was conducted in line with the Helsinki Declaration, as modified at Venice and Hong Kong (1989), and in line with the rules of Good Clinical Practice.
3.3. Selection of the patients

3.3.1. Criteria of inclusion

- Boys or girls aged between 6 and 12 years, not hospitalized.
- The legal guardian of the child having been informed, and having given his written consent.
- A child presenting with predominantly seasonal allergic rhinitis, which was well documented by the history and confirmed with a positive skin test or RAST within the last year.
- A child presenting in the preceding 24 hours, with at least 3 of the 5 following symptoms:
  - sneezing,
  - rhinorrhea,
  - nasal obstruction,
  - nasal pruritus,
  - ocular pruritus.
- The severity of the allergic rhinitis had to be such that at the time of inclusion, the sum of the scores of the five selected symptoms was equal to or greater than 8, each symptom being scored according to the following 4-point scale:
  - 0 = absent,
  - 1 = mild: present but not troublesome,
  - 2 = moderate: troublesome, but not interfering with normal daytime activity or sleep,
  - 3 = severe: disturbing daytime activity and/or sleep.
3.3.2. **Criteria of exclusion**

- Non-seasonal allergic rhinitis requiring the administration of drugs not permitted by the study protocol.

- Asthma requiring administration of systemic or inhaled corticosteroids (> 200 µg/d).

- Atopic dermatitis requiring the administration of systemic or local corticosteroids.

- "Vaso-motor" or infectious rhinitis.

- Infection of the upper respiratory tract, including sinusitis or otitis, present during the 3 preceding weeks.

- Obstructive nasal polyposis.

- High sensitivity to the piperazines (cetirizine, hydroxyzine).

- Clinically significant renal, hepatic, or cardiovascular disease, or any other condition making it inadvisable for the patient to participate in a clinical study.

- Clinically significant laboratory test abnormalities, not related to the condition being studied.

- General infections requiring antibiotic treatment.

- Patients requiring treatment with one or more of the drugs excluded by the study protocol.

- Patients would be excluded if they had used

  during the 6 previous weeks, astemizole or gamma globulins (*).

  during the 2 previous weeks, systemic corticosteroids
  - ketotifen.

  during the previous week, local corticosteroids.

  during the previous 2 days

  ======> • nasal or ocular cromoglycate (*),

  • decongestants,

  • oral antihistamines (other than astemizole or ketotifen).

- Patients undergoing desensitization in the ascending phase.

- Participation in another therapeutic study with another test product in the 3 previous months.

- Recent or predictable changes in the environment: moving house, holidays, etc.

- High chance of not complying with the protocol.

(*): - gamma globulins added at the initializing meeting of the study, in the presence of the investigators.

- Cromoglycate during the 2 previous days instead of during the previous week, criteria changed during the initializing meeting.
3.3.3. **Number of patients**

A minimum of one hundred evaluable children satisfying the selection criteria had to be recruited.

3.4. **Treatments**

3.4.1. **The active treatment tested** (Batch N° 52 R)

The active treatment tested was cetirizine in the form of 5 mg tablets presented in bottles of 20 tablets (1 bottle per week of treatment).

3.4.2. **The reference treatment tested** (Batch N° 53 R)

The reference treatment was a placebo in the form of tablets of identical aspect and taste to the cetirizine tablets, presented in bottles of 20 tablets (1 bottle per week of treatment).
3.4.4. *Dosage*

The dose was 1 tablet morning and evening, to be taken at meal times, for 2 consecutive weeks.

The first tablet had to be taken on the evening of the first visit (visit 1).
3.4.5. Randomization

At the end of the first visit, the patients were randomized into the study. They were attributed a number according to their chronological order of recruitment into the study. This number also served to identify the documents relating to the patients (except for the daily cards, which were numbered differently).

The randomization was balanced within each center.

3.4.6. Concomitant treatments

3.4.6.1. Authorized treatments

The following treatments were allowed to be continued:

- for asthma:
  - theophylline,
  - beta 2 mimetics,
  - inhaled cromoglycate,
  - nedocromil,
  - inhaled corticosteroids ($\leq 200 \mu g/day$).

- for atopic dermatitis:
  - local, non-steroid treatment.

All concomitant treatments had to be noted on the daily evaluation card by the parents, and in the case file by the investigator.

3.4.6.2. Prohibited treatments

The following treatments were forbidden during the course of the study:

- any antihistamines other than the test product,
- decongestants,
- corticosteroids, either systemic or inhaled, roots, at doses of greater than 200 $\mu g/day$,
- sedatives,
- nasal or ocular topical treatments.
3.5. **Evaluation of efficacy**

The efficacy was judged on the basis of the changes in the functional symptoms of the allergic rhinitis as evaluated independently by the investigator in the case file, and by the parents of the patient on the daily evaluation card, both of whom used a similar scoring system.
3.6. Evaluation of safety

3.6.1. Clinical safety

Adverse events were defined as any new or unfavorable events in the health of the patient, observed either by them or by the investigators during the study, whether or not they were related to the test products.

Adverse events were looked for by always asking the same question: "have you observed anything unusual concerning the health of your child?".
3.6.2. Laboratory tests

• Two series of laboratory tests were conducted:
  - the 1st before the beginning of treatment,
  - the 2nd at the end of treatment, whatever the date.

• Each series consisted of:
  - full blood count,
  - platelet count,
  - total bilirubin,
  - transaminases: SGOT (ASAT), SGPT (ALAT),
  - creatinine.

Patients who showed a clinically significant abnormality not related to the condition under study in the first series of laboratory tests were excluded from the study.
3.7.2. Visit 2 - control visit (D8 to D11)

- During this visit, the investigator had to:
  - inquire about possible adverse events,
  - note possible concomitant treatments,
  - note the severity of the rhinitis in the preceding 24 hours,
  - check that the daily evaluation card was correctly filled in: data for the 5 symptoms had to be supplied in at least 80% of cases,
  - recover the bottle of tablets of the test treatment for the first week,
  - check patient compliance: the absorbed dose had to be greater than or equal to 80%, but less than or equal to 120% of the prescribed dose.

- At this visit, patients were excluded from the study in the following cases:
  - any card insufficiency filled in,
  - poor patient compliance,
  - ingestion of a drug forbidden by the protocol,
  - inefficacy of treatment, with the need to prescribe a treatment forbidden by the protocol.

In every patient who dropped out of the study, the investigator had to:

- order the final series of laboratory tests,
- give a global evaluation of the treatment.

- If the patient continued in the study, the investigator gave the family the second course of treatment, after applying onto the case file the detachable part of the identification label for the test treatment.
An appointment was fixed for the final visit on the same day of the subsequent week. If this was impossible, the patient had imperatively to be seen in the next 3 days.

3.7.3. Visit 3 - final visit (D15 to D21)

The controls conducted by the investigator in this visit were exactly the same as those conducted at the previous visit.

In addition, the investigator had to:

- order the final series of laboratory tests,
- give a global evaluation of the treatment.

3.7.4. Special measures

Between treatments, the patient could, in the event of inefficacy or the development of an adverse event, make contact with the investigator. The investigator had to decide whether the treatment should be continued or interrupted. In the latter case, the patient had to return as soon as possible to the investigating center for the final visit.
3.8. Evaluation of the results
3.8.3. *Statistical methodology*

3.8.3.1. *Data collected at the visits*

At each visit, the severity of the rhinitis was evaluated using the highest score for any of the 5 symptoms of rhinitis.

If there was a deviation from the protocol before visit 2, the patient was considered to be not inevaluable for the efficacy of treatment.

If treatment was interrupted at visit 2 or between visit 2 and visit 3, the score at visit 3 was that given on visit 2.

The 2 treatment groups were compared on visits 2 and 3 by the COCHRAN-MANTEL-HAENZEL (C.M.H.) test based on their ranks, and stratified in relation to the baseline (visit 1).

A descriptive analysis based on the mean scores was conducted for the 5 symptoms.
3.8.8.2. Data from the daily cards

**Baseline**: the day before day 1, and day 1.

**Evaluable period**: from day 2 to the last evaluable day.

For each patient and each day, the highest score for any of the 5 symptoms was selected. For the whole of the evaluable period for each patient, the cumulated relative distribution frequencies of the maximal scores were calculated, giving, for each patient, the following variables:

1. percentage of days with a score = 0 (PDS0).
2. percentage of days with a score ≤ 1 (PDS1).
3. percentage of days with a score ≤ 2 (PDS2).

The medians for the 2 groups for these 3 variables were compared using WILCOXON’s rank test.

The variable PDS1 constituted the main criterion of judgement for efficacy.

A descriptive analysis based on the mean scores was conducted for the 5 symptoms.

3.8.3.3. Global evaluation

A Mann-Whitney test was conducted to compare the distributions of the groups.

3.8.3.4. Adverse events

The proportions of adverse events in the 2 groups (after regrouping by class) were compared using the chi-squared test.

A similar analysis was conducted for the laboratory test abnormalities.

3.8.3.5. Threshold of significance

The threshold of significance retained was 5%, and the tests were bilateral.
4. RESULTS

4.1. Rhythm of recruitment and regional pollen counts

- In total, 92 subjects were included.
• The comparison between the rhythm of inclusions and the pollen count data was conducted using the following breakdown:

- Lyon with N = 61 inclusions,
- Grenoble (+ Chambéry) with N = 17 inclusions,
- Rouen with N = 14 inclusions.

Tables 4.1.a and 4.1.b recapitulate the pollen counts (gr/m³) and the rhythm of inclusions, both by region and by week.

Figures 4.1.a, 4.1.b and 4.1.c represent, by region and by week, the comparative changes in the rhythm of inclusions as compared to the grass pollen counts.

• This comparison was conducted taking into account only the rate of inclusions as compared to the grass pollen counts alone, these being in effect both the most frequently present taxon during the study and the most frequently implicated allergen in the patients (for this purpose, further pollen counts for the Lyon region were obtained directly from the Institute Pasteur).

Finally, figure 4.1.d summarizes the general sum of inclusions, in comparison to the regional grass pollen counts.

An analysis of these tables and figures brings out the following points:

- the effective inclusion period extended from mid-May 1990 to mid-July 1990 (19 July for Lyon, 21 June for Grenoble, 12 July for Rouen), and there is in general a good correlation between the changes in the regional grass pollen counts and the inclusion rate, with the exception of Bordeaux where, despite the high pollen count, no inclusions were recorded.

- Although the peaks of inclusion are usually seen at the same times as the increases in the pollen count, it should be noticed that the first period with a large number of inclusions in the Lyon region does not correspond to a peak in the grass pollen count. This can be explained, however, by the fact that the main investigators in this region had preselected in advance their first patients and they entered into the study as soon as it was effectively commenced.

- The interruption of the inclusions, starting from mid-July, corresponds both to the fall-off in the pollen counts, and to the summer vacations.

- The last two inclusions, registered in September in Lyon, correspond to the late pollen period (ambrosia) specific to this region.
4.2. Description of the population studied

4.2.1. Number of patients included

In the study, a total of 47 patients were included in the placebo group.
<table>
<thead>
<tr>
<th>Cetirizine group (N = 44)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group (N = 47)</td>
<td>N = 91</td>
</tr>
</tbody>
</table>
4.3. Homogeneity of the 2 groups

4.3.1. Demographic characteristics

The 2 groups were comparable from the point of view of the demographic data (sex, age, height and weight).

<table>
<thead>
<tr>
<th></th>
<th>CETIRIZINE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>SEX</td>
<td>Male</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>AGE (ans)</td>
<td>Mean</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Minimum/Maximum</td>
<td>(6 - 12)</td>
</tr>
<tr>
<td>HEIGHT (cm)</td>
<td>Mean</td>
<td>132.9</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>Minimum/Maximum</td>
<td>(108 - 155)</td>
</tr>
<tr>
<td>WEIGHT (kg)</td>
<td>Mean</td>
<td>30.4</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>Minimum/Maximum</td>
<td>(16.2 - 47.8)</td>
</tr>
</tbody>
</table>

4.3.2. History and physical examination

The two groups were also comparable from the point of view of the history and physical examination. The main abnormalities detected on clinical examination came under the section "Nose and Sinuses", where all the patients naturally showed symptoms, and under the section "Eyes", where 31 patients from the cetirizine group and 41 patients from the placebo group showed associated ocular signs.
4.3.3. *History of the present illness*

4.3.3.1. *Duration of the seasonal allergic rhinitis*

The mean duration of the rhinitis was comparable in both groups: it was 2.3 years in the cetirizine group and 2.6 years in the placebo group. The breakdown by the number of years of the disease is shown in the histogram below.

![Histogram showing duration of seasonal allergic rhinitis](chart.png)

<table>
<thead>
<tr>
<th>Number of years with disease</th>
<th>Cetirizine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>25% 20% 15% 10% 5% 0%</td>
<td>5% 10% 15% 20% 25%</td>
</tr>
<tr>
<td>&lt;2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.3.3.2. *Documentation of the allergen*

For all the patients, the seasonal allergic rhinitis was well documented with skin tests and/or the RAST.

The main allergens responsible were identical in both groups. They were either grass pollens or cereals, in this order:
Grass pollens:

- 83 patients had a positive (+ +) or highly positive [++] skin test for grass pollens (N = 79) or dactyls (N = 4), a result which is generally confirmed by the RAST. Note, however, patient 509/02 (placebo group), in whom the positive skin test (+ +) was not confirmed by the RAST (0).
In total, 90 of the 91 patients had documented allergy to grass pollens, the allergen which was preponderant during the period of the study.

**Cereals:**

All 59 patients who had the skin test against this allergen had a positive or very positive result, when it was conducted, confirmed by the RAST.
4.3.3.3. Previous treatments

37 patients from each group had already received one or more treatments for their rhinitis.

The details are shown in the tables below:

<table>
<thead>
<tr>
<th>PREVIOUS TREATMENTS</th>
<th>CETIRIZINE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>YES</td>
<td>37</td>
<td>84.1</td>
</tr>
<tr>
<td>NO</td>
<td>7</td>
<td>15.9</td>
</tr>
<tr>
<td>TOTAL</td>
<td>44</td>
<td>100.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PREVIOUS TREATMENTS</th>
<th>CETIRIZINE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>29</td>
<td>65.9</td>
</tr>
<tr>
<td>General corticosteroids</td>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td>Local corticosteroids</td>
<td>5</td>
<td>11.4</td>
</tr>
<tr>
<td>Preventive treatments</td>
<td>14</td>
<td>31.8</td>
</tr>
<tr>
<td>Desensitization</td>
<td>5</td>
<td>11.4</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
<td>25.0</td>
</tr>
</tbody>
</table>
4.3.3.4. Severity of the rhinitis

The severity of the rhinitis, as evaluated by the investigator on D0, was comparable in both groups, both from the point of view of the maximal score, and for each of the symptoms studied.

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>CETIRIZINE (N = 44)</th>
<th>PLACEBO (N = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
<td>STANDARD DEVIATION</td>
</tr>
<tr>
<td>Sneezing</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>1.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>2.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Nasal pruritus</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Ocular pruritus</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>MAXIMAL SCORE</td>
<td>2.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

The same was true for the initial auto-evaluation of the patients for the 2 days preceding the first day of treatment (D0-D1), which was also in line with the judgment of the investigator.

<p>| MAXIMAL             | CETIRIZINE         | PLACEBO         |</p>
<table>
<thead>
<tr>
<th>SCORE</th>
<th>N</th>
<th>MEAN</th>
<th>STANDARD DEVIATION</th>
<th>N</th>
<th>MEAN</th>
<th>STANDARD DEVIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>D0</td>
<td>42</td>
<td>2.7</td>
<td>0.5</td>
<td>45</td>
<td>2.7</td>
<td>0.4</td>
</tr>
<tr>
<td>D1</td>
<td>44</td>
<td>2.4</td>
<td>0.7</td>
<td>47</td>
<td>2.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The results are illustrated in the diagram on the next page.
### Symptoms on D0

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cetirizine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 1 0</td>
<td>1 2</td>
</tr>
<tr>
<td>Sneezing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular pruritus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maximal score (case file)

Maximal score (auto-evaluation)  
D0:  
D1:
4.4. Analysis of efficacy

4.4.1. Principal criterion

The percentage of days with a maximal score equal to or less than 1 (PJD1), for whatever symptom, as scored by the patients on the daily auto-evaluation cards, constituted the principal criterion of judgment.

The mean was 29.7 % (standard deviation = 33 %) in the cetirizine group and 26.2 % in the placebo group (standard deviation = 27.2%). The difference (p = 0.8) was not statistically significant while slightly in favor of cetirizine.

4.4.2. Other criteria obtained from the auto-evaluation data

The mean percentage of days with a maximal score equal to or less than 2 (PJD2) was not statistically significant (p = 0.7) between the cetirizine group (71 %) and the placebo group (70 %).

In contrast, the mean percentage of days with a maximal score equal to 0 (PDS0), in other words the absence of any symptoms, was in favor of the cetirizine group: 5.6 % versus 1.8 %. This result, however, is not statistically significant (p = 0.07).

4.4.3. Maximal score (investigator)

In both groups, the mean maximal score (the most severely scored symptom) improved over time.

<table>
<thead>
<tr>
<th>SCORE MAXIMUM</th>
<th>CETIRIZINE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>MEAN</td>
</tr>
<tr>
<td>Visit 1</td>
<td>44</td>
<td>2.7</td>
</tr>
<tr>
<td>Visit 2 (*)</td>
<td>44</td>
<td>2.0</td>
</tr>
<tr>
<td>Visit 3 (**)</td>
<td>44</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Cochran-Mantel-Haenszel test based on the scores and stratified in relation to the baseline (visit 1)

(*) p = 0.71
(**) p = 0.068
However, in the cetirizine group, the improvement observed at the second visit continued up to the third visit, unlike the placebo group, in whom the score returned to a greater degree of severity.
4.4.4. Total score (investigator)

The total score for the 5 symptoms studied confirmed the previous result: this score improved more favorably in the cetirizine group (a change of 4.9 points) than in the placebo group (a change of 3.6 points).
4.4.5. *Drop-outs due to inefficacy*

Three patients (6.8%) from the cetirizine group versus 7 (14.9%) from the placebo group dropped out from the study because of the inefficacy of the treatment; in other words, twice as frequently as the placebo group. However, this difference is not statistically significant ($p = 0.32$).

4.4.6. *Global evaluation of the treatment*

The global evaluation of the treatment by the investigator confirmed the efficacy seen in the cetirizine group.

<table>
<thead>
<tr>
<th>GLOBAL EVALUATION OF THE TREATMENT</th>
<th>CETIRIZINE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Aggravation</td>
<td>4</td>
<td>9.3</td>
</tr>
<tr>
<td>No change</td>
<td>6</td>
<td>14.0</td>
</tr>
<tr>
<td>Slight improvement</td>
<td>8</td>
<td>18.6</td>
</tr>
<tr>
<td>Good improvement</td>
<td>17</td>
<td>39.5</td>
</tr>
<tr>
<td>Excellent improvement</td>
<td>8</td>
<td>18.6</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>43</td>
<td>100.0</td>
</tr>
</tbody>
</table>

This result is statistically significant ($p = 0.002$) and is illustrated in the diagram below.
4.5. Analysis of safety

4.5.1. Adverse events

Note first of all that an adverse event was described as "any new and unfavorable event concerning the health of the patient, observed by the patient and/or the investigators during the study, whether or not related to the test products."

13 adverse events were seen in a total of 8 patients in the cetirizine group, versus 29 adverse events in 21 patients in the placebo group.

<table>
<thead>
<tr>
<th>INCIDENCE OF ADVERSE EVENTS</th>
<th>CETIRIZINE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>36</td>
<td>81.8</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>13.6</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>44</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Chi-squared test: P=0.007
(Presence/Absence of adverse events)
## ADVERSE EVENTS

### NUMBER AND INCIDENCE (%)

<table>
<thead>
<tr>
<th>ANATOMICAL CLASSIFICATION</th>
<th>CETIRIZINE GROUP N = 44</th>
<th>PLACEBO GROUP N = 47</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>(%)</td>
</tr>
<tr>
<td><strong>The body in general</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. Asthenia</td>
<td>1</td>
<td>(2,3)</td>
</tr>
<tr>
<td>. Headaches</td>
<td>3</td>
<td>(6,8)</td>
</tr>
<tr>
<td>. Abdominal pains</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>. Fever</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Gastrointestinal system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. Diarrhea</td>
<td>3</td>
<td>(6,8)</td>
</tr>
<tr>
<td>. Vomiting</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>. Digestive system</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. Epistaxis</td>
<td>1</td>
<td>(2,3)</td>
</tr>
<tr>
<td>. Cough</td>
<td>2</td>
<td>(4,5)</td>
</tr>
<tr>
<td>. Tonsilitis</td>
<td>1</td>
<td>(2,3)</td>
</tr>
<tr>
<td>. Asthma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Skin and its appendages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. Urticaria (to pollen)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sense organs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. Visual symptoms</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>. Infection of the eyelid</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>. Conjunctivitis (to pollen)</td>
<td>1</td>
<td>(2,3)</td>
</tr>
<tr>
<td>. Otitis</td>
<td>1</td>
<td>(2,3)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>13</td>
<td>(29,5)</td>
</tr>
</tbody>
</table>
4.5.2. *Laboratory tests*

Overall, no major abnormality was seen in the various laboratory tests conducted in either treatment group. Usually, the minor abnormalities reported involved parameters whose values fell outside the "norms" for the laboratory concerned, but of no clinical significance. In all these cases, the value was just above or below the normal theoretical value. However, several children in both groups showed, at the time of the initial series of investigations, a clinically significant eosinophilia (greater than 500/mm³), but this was judged to be related to the seasonal allergic rhinitis, and remained high at the time of the final series of laboratory tests.
5. DISCUSSION

The results of this study merit a certain number of comments.

5.1. Methodology
The choice of the principle criterion for the evaluation by the patient is debatable, and the absence of any significant differences observed perhaps reflects the lack of sensitivity of the criterion selected. We probably do not have sufficient experience with this criterion to be sure of its reliability.

- In contrast, the global evaluation by the investigator is a criterion increasingly taken into account in the evaluation of therapeutic trials. Although it is subjective, it reflects coherently the combined appreciation of the efficacy and safety of the test product.

5.2. Results

The fact that several clearly beneficial effects of cetirizine over placebo were not demonstrated in this study led us to investigate a certain number of points:

- The treatment bottles recovered from the investigators were checked to see if there was an agreement between the initial randomization list and the treatments effectively attributed. The quantity of the active principle was also checked.

- Patient compliance with the treatment was rechecked patient by patient to see if there was a proper agreement between the number of unused tablets recovered (shown in the control chart of the test products, and the corresponding figures in the case files).

- The word processing and statistical computing procedures were rechecked. No errors were demonstrated by these control procedures.

- The meteorological conditions prevailing over the main part of the study (cf. appendix) probably introduced a bias in the evaluation of the progress of the scores. In the second half of May, there were several rainy periods for between 8 and 10 days in Lyon and Chambéry, and in the month of June it rained for between 15 and 20 days in all three regions (Lyon, Chambéry, Grenoble). As there was no daily pollen count in all the regions, the comparative changes in the rainfall and pollen counts could not be checked.

It is, however, legitimate to think that the symptoms could have been affected by these meteorological changes, and were affected by these rainy periods, reducing the real observable difference between the cetirizine and placebo groups.
However this may be, the absence of any significant changes observed in the principle criterion (PDS1) must be combined with the finding of a favorable global tendency observed in the cetirizine group, and in particular in:

- the incidence of premature drop-outs for inefficacy (twice as frequent on placebo),
- the appearance of new clinical symptoms and signs related to the disease under observation (6 times more frequent on placebo),
- the global evaluation by the investigator, highly significantly (p = 0.002) in favor of cetirizine.

6. CONCLUSION

The object of this phase III, multicenter (15 centers), double-blind study of cetirizine versus placebo was to confirm the therapeutic efficacy of cetirizine at a dose of 10 mg/day divided in 2 daily doses, and to complete our knowledge concerning its safety in children between 6 and 12 years of age suffering from seasonal allergic rhinitis and treated for 2 weeks.

92 children were included during the pollen season between May and September 1990. 91 were analyzable, 44 in the cetirizine group and 47 in the placebo group.

The results of the previously determined principal criterion of judgment, namely the percentage of days with a maximal score (whatever the symptom) equal to or less than 1 on daily auto-evaluation by the patients did not show any significant difference between the 2 groups.

However, there were several arguments in favor of the cetirizine group:

- the percentage of days with a maximal score equal to 0 (absence of any symptoms) on daily auto-evaluation was 3 times higher in the cetirizine group (5.6 % versus 1.8 %).

- the mean maximal score (scored by the investigator) between visits 1 and 3 improved more in the cetirizine group (from 2.7 to 1.8) than in the placebo group (from 2.8 to 2.2), with a similar change in the mean total score, which improved by 4.9 points in the cetirizine group, versus only 3.6 points in the placebo group.

- the incidence of premature drop-outs from the study due to inefficacy, although low, was twice as great in the placebo group (14.9 %) as in the cetirizine group (6.8 %).

- the appearance of new symptoms related to the disease under investigation was 6 times greater in the placebo group (25.5%) than in the cetirizine group (4.5 %).
As regards the adverse events (any new or unfavorable events), these were twice as frequent in the placebo group (28 events in 21 patients) as in the cetirizine group (13 events in 8 patients). However, if we exclude those events in which the relationship was excluded from the beginning (no relation) by the investigator, the incidence of these events is comparable in the 2 groups: 9 events in 6 patients in the cetirizine group versus 7 events in 6 persons in the placebo group.

The vast majority of these events were minor. No cases of somnolence were reported, and no serious adverse event was reported.

The laboratory tests reported did not show any remarkable abnormalities which appeared on treatment.

In total, the global evaluation of the treatment by the investigator was clearly in favor of the cetirizine group (p = 0.002).