STUDY A 132 - CLINICAL REPORT RRCE92L2503

DOUBLE BLIND, RANDOMISED STUDY, IN THREE PARALLEL GROUPS,
TO COMPARE THE EFFICACY AND TOLERANCE OF CETIRIZINE (5, 10 or 15 mg b.i.d
ACCORDING TO BODY WEIGHT), KETOTIFEN (1 mg b.i.d) AND PLACEBO IN THE
TREATMENT OF PERENNIAL ALLERGIC ASTHMA IN CHILDREN AND ADOLESCENTS
(Protocol PCF88F101)

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SUMMARY

The efficacy and safety of cetirizine (5, 10 or 15 mg 2x/day according to body weight) were compared to those of ketotifen (1 mg 2x/day) and placebo in the treatment of mild perennial allergic asthma (grades 2 or 3 according to K. Aas) in children and adolescents.

After an observation period of 2 weeks with placebo 2x/day (single blind) and $\beta_2$-agonists by inhaler (in case of asthma), seventy six patients were randomized in the study: 25 patients received cetirizine, 27 patients received ketotifen and 24 patients received placebo.

The treatment was to be taken during 4 months.

The FEV1 and asthma symptoms were assessed regularly by the investigator (6 visits, one after 2-week interval, the others at 4-week interval). Asthma symptoms and inhaled $\beta_2$-agonists consumption as well as other anti-asthma drugs were recorded daily by the patients on special daily record card. Morning and evening peak flow measurements were also recorded in the same way by the patients.

The three treatments were not different from each other during baseline and after treatment.

One efficacy variable, computed from the daily record cards was chosen as main efficacy variable: the frequency of days and/or nights with asthma (FAST).

For FAST, the medians of the improvements observed for the total period of treatment as compared to baseline were the following: 5.9 % in the cetirizine group (baseline = 35.7 %), 6 % in the placebo group (baseline = 37.9 %) and 11.8 % in the ketotifen group (baseline = 26.7 %). The differences were neither statistically nor clinically significant.

All other variables, called secondary efficacy variables recorded at home on the daily record cards or at the visits by the investigator, show no consistent significant differences between the three treatment groups.

The incidence of adverse events was higher in the ketotifen group (13/27 patients) than in the
cetirizine (7/25 patients) or placebo group (3/24 patients), (global comparison p = 0.014, comparison ketotifen placebo p = 0.004, other comparisons are not statistically significant).

The most frequent adverse event in the cetirizine group was pharyngitis, one case of sedation was also reported in the cetirizine group.

Appetite increase was the most frequent adverse event in the ketotifen group.

No clinically relevant treatment effect on laboratory measurements were seen.
I. INTRODUCTION

Cetirizine, a powerful and selective antihistamine H₁, with a rapid and prolonged action (1, 2) is marketed in all EEC countries for the treatment of allergic rhinitis and urticaria.

Pharmacoclinical studies in skin and lung were conducted with cetirizine (using doses ranging from 10 to 30 mg per day).

These showed:
• inhibition of the eosinophil migration in the delayed hypersensitivity reaction induced by an antigen in the skin (3)
• inhibition of bronchospasm induced by histamine (4)
• encouraging results in the model of bronchospasm induced by pneumoallergens (5)
• inhibition of the eosinophils accumulation in the bronchial lavage 24 hours after allergic bronchoprovocation (6).

Controlled clinical studies suggest that cetirizine could (partially) replace theophylline (7) or inhaled corticosteroids (200 - 1000 μg per day (8)) in the treatment of perennial asthma.

This study was carried out to assess the effect of cetirizine in children with mild perennial asthma, by comparing it with ketotifen and placebo.

Objective of the study
1. To compare the efficacy of cetirizine, ketotifen and placebo, administered as prophylactic treatment to patients with perennial atopic asthma (reduction of the asthma frequency, reduction of inhaled β₂-agonists consumption).
2. To compare the safety of the three treatments (adverse events, laboratory tests).
II. METHODS

1. Study plan
   This was a double-blind multicentre study, each centre randomizing its patients into three parallel groups: one cetirizine group (5 mg, 10 mg or 15 mg twice daily according to body weight), one ketotifen group (1 mg twice a day) and one placebo group (one tablet twice a day).
2. Selection of the patients

2.1 Inclusion criteria

- male or female
- aged between 5 and 16 years
- weight not less than 15 kg
- known by the investigator for at least 6 months
- a well-documented history of atopic, perennial asthma for which they have been prescribed and using β₂-agonists by inhaler, at a fixed dose and/or on demand, over a period of at least two months prior to their inclusion
- a history of asthma which include symptoms indicating typical paroxysmal, recurrent attacks of expiratory dyspnoea with wheezing; the periodicity of these attacks should correspond to, or have conformed to the Grade 2 or Grade 3 of Kaas pattern at the time of starting their present treatment (see Appendix II)
- a strongly positive prick or intradermal test (diameter of the wheal is 5 mm or more) in response to challenge with a perennial allergen such as dermatophagoides, dogs and casts, fungi, or a positive RAST to a perennial allergen
- a FEV₁, performed between attacks, which is 80 % or more of the predicted value; a FEV₁ of 50 to 80 %, should be reversible after use of a β₂-agonist by inhaler, before starting the study.

Oral informed consent was obtained from the parents.
2.2 Exclusion criteria

- pregnancy or females at risk
- asthma falling into categories 1, 4 or 5 at the time the patient's current drug treatment was prescribed, or into categories 4 or 5 while they were being started
- asthma which required treatment other than β₂-mimetics by inhaler, during the "washout" period
- asthmatic attack severe enough to warrant hospitalisation within the preceding six months
- dependence on corticosteroids, and treatment at a dose > 200 μg/day on a steroid inhaler
- abnormal haematology or biochemistry at preselection (visit 1)
- hepatic insufficiency, renal or cardiac failure, a severe chest infection, or any infection other than an ENT or URTI
- abnormal chest X-Ray i.e. showing thoracic deformity, tracheal compression, emphysema, bronchiectasis, etc...
- mucoviscidosis, observed gastro-oesophageal reflux, difficulties with swallowing, severe atopic dermatitis which cannot be controlled with topical therapy, severe allergic rhinitis which cannot be controlled with topical therapy
- positive RAST or prick test to tree or grass pollen if, at the time of inclusion, the patient has an exacerbation of his symptoms
- chronic urticaria, or some other skin disorder treated with antihistamines, unless this treatment has been discontinued at the preselection visit
- patients unable to tolerate ketotifen or hydroxyzine (Atarax)
- patients with risk of non compliance, whether for geographical, mental or other reasons
- patients with lifestyle or occupation which will put the patient at particular risk from possible sedation due to the medication.

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3. **Treatments**

3.1 **Study products and dosage schedule**

- **during the two-weeks baseline (period 1) in single blind**
  
  - placebo: scored **round** tablets, morning and evening

- **during periods 2 to 5 in double blind**
  
  - cetirizine: scored **oblong** 10 mg tablets
  - placebo of cetirizine: scored **oblong** tablets of same aspect
  - ketotifen: 1 mg capsules
  - placebo of ketotifen: capsules of same aspect.

The dose of cetirizine and corresponding placebo was determined on the basis of the bodyweight at inclusion, and remained unchanged during the whole period of the study:

- 15-30 kg: 10 mg per day, i.e. 1/2 tablet morning and evening
- 30.1-50 kg: 20 mg per day, i.e. 1 tablet morning and evening
- > 50 kg: 30 mg per day, i.e. 1 1/2 tablet morning and evening.

The dose of ketotifen was 2 mg per day for all the patients.

- To ensure compliance with the double-blind design of the study, the "double dummy" technique was used.
  - the patients in the cetirizine group took the cetirizine tablets and the placebo capsules
  - the patients in the ketotifen group took the placebo tablets and the ketotifen capsules
  - the patients in the placebo group took the placebo tablets and the placebo capsules.
3.2 Washout periods
Before inclusion \((V_2)\) patients had to be off following treatments for the following periods:
- one month for astemizole and systemic corticosteroids (i.e. 15 days before \(V_1\))
- two weeks for:
  - cromoglycate
  - ketotifen
  - inhaled steroids \(\leq 200 \mu g\) per day
  - oral \(\beta_2\)-agonists
  - theophylline
  - antihistamines other than astemizole.

3.3 Concomitant treatment
Only inhaled \(\beta_2\)-agonists were permitted, on demand in case of an asthma attack.
5. Evaluation of efficacy

5.1 Assessments made by the investigator at the visits

- FEV1: expressed as a % of the predicted value.
- Specific physical examination
  - Chest:
    - cough, dyspnoea and wheezing, on a 4-point scale:
      0 = absent, 1 = mild, 2 = moderate, 3 = severe
    - presence or absence of infection of the upper respiratory tract
  - Skin:
    - atopic dermatitis and urticaria on a 4-point scale:
      0 = absent, 1 = mild, 2 = moderate, 3 = severe
  - E.N.T.:
    - rhinitis and allergic conjunctivits, also on a 4-point scale
    - presence or absence of E.N.T. infection
  - Reactivity to metacholine: optional
    - measurement of the PC20 and PD20 at visits 2 and 5 (or the last visit in case of withdrawal from the study), if the respiratory condition of the patient allows.

- Evaluation of the activity of the treatment at the last visit
  This evaluation was made for asthma, and possibly rhinitis, atopic dermatitis and urticaria, on 5-point scales: excellent, good, moderate, poor, very poor.

5.2 Assessments made by the patients at the visits

- Evaluation of the quality of life, on visits 1 to 6 (or on the last visit in the event of premature withdrawal from the study). This evaluation was made using non-graduated 100 mm visual analogue scales (see Appendix III).
5.3 **Assessments made by the patient at home**

Every day, the patients had to evaluate or measure:
- peak expiratory flow rate in the morning and the evening (the best of three attempts)
- diurnal and nocturnal asthma on two 4-point scales*
- consumption of inhaled β₂-agonists (number of puffs)
- intake of any other drug.

All this information had to be carefully noted on the daily record cards which were given to the patients at each visit.

5.4 **Withdrawals from the study for inefficacy**

See item 8.

* **Nocturnal asthma**

0 = no asthma, slept well
1 = woke once because of asthma
2 = woke several times because of asthma
3 = did not sleep because of asthma

**Diurnal asthma**

0 = no asthma
1 = wheezing, occasional cough, some shortness of breath but not incapacitating
2 = wheezing, shortness of breath, irritating cough, impairing the usual activities
3 = severe asthma, unable to conduct usual activities
6. **Evaluation of safety**

6.1 **Adverse events or special events** reported spontaneously by the patients at the visits and/or on the daily record cards supplied to the patients.

All adverse events were described by the investigator regarding their incidence, severity (mild, moderate, severe), duration and causal relationship to the test drug (no, possible, yes).

6.2 **Withdrawals from the study due to adverse events**

See item 8.

6.3 **Laboratory tests**

Blood tests were performed at visit 1 and at the last visit:

- red blood cells
- hemoglobin
- hematocrit
- white blood cells + differential count
- total proteins
- SGPT/SGOT/gamma GT
- urea/creatinine
- total bilirubin
- triglycerides
- total IgE
9. **Statistical analysis**

9.1 **Analysis of efficacy**
An intention-to-treat analysis of efficacy was done including all randomized patients who received a treatment (cetirizine, ketotifen or placebo) at visit 2, and who had at least one intake after visit 2.
9.1.2 Statistical methods

9.1.2.1 A descriptive statistical analysis of all variables was performed.

9.1.2.2 Global tests for independent samples were first used for comparing the three treatments.

If a statistically significant difference between them was seen, multiple comparisons between treatment (cetirizine versus placebo, ketotifen versus placebo, cetirizine versus ketotifen) were performed.

9.1.2.3 All comparisons were made on the differences between initial status (= baseline) and time considered:

Visits
At visits 3, 4, 5 and 6, taking \( V_2 \) as baseline.

Daily record cards
For the periods (i.e. interval between 2 visits) 2, 3, 4 and 5 taking period 1 as baseline.

The overall period was also defined = interval between visit 2 and the last evaluable day of the study.

9.1.2.4 Tests used

<table>
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<th>variable type</th>
<th>global tests (3 groups)</th>
<th>multiple comparisons (2 by 2)</th>
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<tr>
<td>nominal</td>
<td>Fischer exact test</td>
<td>CMH</td>
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<td></td>
<td>Cochran Mantel Haenzel test (CMH) if baseline adjusted comparisons</td>
<td></td>
</tr>
<tr>
<td>ordinal</td>
<td>CMH</td>
<td>CMH</td>
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<tr>
<td>continuous</td>
<td>Kruskal-Wallis</td>
<td>Wilcoxon 2-sample test</td>
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9.1.2.5 *Estimation of missing data*

When a patient left the study due to ineffectiveness or adverse events, the results at the time of withdrawal were used as an estimate for the missing values for the subsequent visits and periods (except for the total period).

9.1.2.6 *Statistical significances*

All the tests were two tailed at the 5% level of significance.

9.2 *Analysis of safety*

9.2.1 *Adverse events*

- All reported adverse events were classified according to COSTART (third edition, 1989).
- A descriptive analysis of all reported adverse events classified by COSTART, by severity and by relationship to the test drug was done.
- The frequency distributions by treatment of the number of adverse events reported by the patients were compared by the Cochran-Mantel-Haenszel test.

If the same adverse event was reported on several occasions by one patient, only one was retained, with the highest severity score and the strongest relationship to the test drug.

9.2.2 *Laboratory blood tests*

Laboratory tests were performed at first and last visit.

Units and normal ranges of laboratories that performed blood analyses varied from center to center. Therefore, the measured values of laboratory tests were standardized to allow a non-parametric analysis of all the patients, by using a three-categories scale "status" (independent of normal range and units, defined below.

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status = - measured value below the lower limit of the normal range;
  0 measured value within the normal range;
  + measured value above the upper limit of the normal range.

- **Descriptive analysis**
  - Individual data by patient for all laboratory variables: measured values at each lab, lower and upper limit of the normal range, units and status (-, 0, +) at each lab;
  - frequency distribution of status at each lab;
  - frequency distribution of status at last visit stratifying for status at baseline (visit 1).

- **Statistical analysis**
  - Cochran-Mantel-Haenszel test, computed on the ranks and stratified by status at baseline, on variable status at last visit.
III. RESULTS
The study was conducted in time with the Helsinki Declaration and after review by the Ethics Committees.

1. Timing
The study took place from October 2, 1989 to June 6, 1991 and started one year later than foreseen; this was due to the delay taken by the Ethics Committee to review the protocol.

2. Sample description
2.1 Sample size
2.1.1 Total number of patients
83 case report forms, corresponding to 83 patients were filled in for the whole study by the 7 investigators who participated in the study (see Appendix I). Seven patients were not randomized in the trial (actual study) either because of ineligibility at V₁ or V₂ or because they were lost of view after V₁. The list of the 7 patients who did not participate in the actual is given in Appendix IV. These
2.2 **Demography**

76 patients (61 boys and 15 girls) aged between 5 and 16 years and weighing between 17.5 and 80.0 kg were selected and included in the study. A description of the patients is given in Table I. Girls were recruited in greater proportion in the ketotifen group (33 %) than in the placebo group (12.5 %) and in the cetirizine group (12.0 %).
All patients had a documented allergy to a perennial allergen (positive PRICK or RAST test). Mean duration of asthma was longer in the ketotifen group (7.3 years) than in the placebo group (5.6 years) and in the cetirizine group (5.8 years).

2.3 **Description of the baselines** (Tables II and III)

Although the differences were mainly minor, it is worth remarking that the patients in the cetirizine group were on average less severely affected than in the other two groups except for the frequency of asthma during day and/or night (FAST).
5. **Analysis of efficacy**

5.1 **General remarks**

Before breaking the code, FAST considered to be clinically the most relevant, was chosen as primary efficacy variable.

All other variables were considered as secondary efficacy variables.

5.2 **Primary efficacy variable, FAST : frequency of days and/or nights with asthma (Table VI, figure 1)**

FAST improved in the three groups during study. Baseline mean (median) FAST was 31.1 % (35.7) in the cetirizine group, 40.2 % (37.9) in the placebo group and 32.9 % (26.7) in the ketotifen group.

For the total period, mean (median) FAST was 19.2 % (9.5) in the cetirizine group, 27.8 % (20.3) in the placebo group and 20.3 % (9.8) in the ketotifen group.

Global comparison of the differences between total period and period 1 (medians = - 5.9%, - 6%, - 11.8% respectively in the cetirizine, placebo and ketotifen groups) was statistically not significant (p = 0.985). All details are given in Table VI.

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5.3 Secondary efficacy variables

5.3.1 Morning peak flows (AMPF, Table VII, figure 2)
AMPF improved in the three groups.
Baseline AMPF (median) was 242 l/min in the cetirizine group, 229 l/min and 217 l/min respectively in the cetirizine, placebo and ketotifen groups.
Global comparison of the differences between total period and period 1 (medians = 14.1, 15.7 and 8.3 l/min respectively in the cetirizine, placebo and ketotifen groups) was not significant (p = 0.651).
Some details are given in Table VII and full details in statistical report.

5.3.2 Evening peak flows (AEPF, Table VIII, figure 3)
AEPF improved in the three groups. Baseline AEPF (median) was 252 l/min the cetirizine group, 243 l/min in the placebo group and 224 l/min in the ketotifen group.
Global comparison of the differences between total period and period 1 (medians = 16.0, 14.5 and 13.9 respectively in the cetirizine, placebo and ketotifen group) was not significant (p = 0.652).
Some details are given in Table VIII and full details in statistical report.

5.3.3 Asthma at night (AALN, AGALN and FALN, Tables IX, IX-X)
6/25 patients in the cetirizine group (24 %), 2/24 patients in the placebo group (8 %) and 5/27 patients in the ketotifen group (19 %) never suffered from asthma at night.
Therefore, the average asthma score at night (AALN) is of minimal interest and will not be detailed in this report: AALN was very low throughout the study in the three groups. Full details are given in the statistical report.

AGALN did not change much during study. Median value at baseline and total period was 1.0 in the three groups.
Global comparison of the difference between total period and period 1 (medians = 0.0 in all groups) was not statistically significant (p = 0.254).
To be noticed a statistically significant difference in favour of cetirizine as compared to ketotifen at period 3 ($p = 0.021$). Some details are given in Table IX and full details in statistical report.

FALN improved in all groups during the study.
Baseline mean (median) FALN was 18.6 % (7.7) in the cetirizine group, 25.2 % (20.7) in the placebo group and 21.2 % (15.4) in the ketotifen group.
For the total period, mean (median) FALN was 12.7 % (4.4) in the cetirizine group, 19.2 % (8.8) in the placebo group and 11.9 % (4.5) in the ketotifen group.
Global comparison of the differences between total period and period 1 (medians = 0.0, -1.4, and -4.0 respectively in the cetirizine, placebo and ketotifen group) was not statistically significant ($p = 0.719$). Some details are given in Table X and full details in statistical report.

5.3.4 Asthma during the day (AATD, AGATD and FATD, Tables XI-XII)
As for the asthma at night a lot of patients did not have any asthma symptoms during the day for the whole study period: 3/25 patients in the cetirizine group (12 %), 2/24 % in the placebo group (8 %) and 4/27 in the ketotifen group (15 %). For this reason, AATD is not detailed here; values were very low throughout the study, no statistical differences were seen (details to be found in the statistical report).

AGATD did not change during study.
Median value at baseline and total period was 1.0 at baseline and total period was 1.0 in the three groups. Global comparison of the differences between global period - period 1 (medians = 0.0 in the three groups) was not significant ($p = 0.860$). See some details in Table XI.

FATD improved in the three groups during the study. Baseline mean (median) FATD was 20.9 % (7.1) in the cetirizine group, 33.2 % (34.5) in the placebo group and 26.2 % (20.0) in the ketotifen group.
For the total period mean (median) FATD was 14.5 (8.1) in the cetirizine group, 23.9 % (14.5) in the placebo group and 16.5 (4.5) in the ketotifen group.
Global comparison of the differences between total period and period 1 (medians = 0, -3.5, -7 respectively in the cetirizine, placebo and ketotifen groups) was statistically not significant (p = 0.253). Some details are given in Table XII, and full details in statistical report.

5.3.5 Medication for asthma (APUF, AGMED and FMED, Tables XIII-XV)
Median value of APUF was very low at baseline and during the whole study (less than 0.5 puff/day!); moreover 5/25 patients in the cetirizine group (20%), 3/24 in the placebo group (14%) and 3/27 in the ketotifen group (11%) never had recourse to β₂-agonists by inhaler.
Global comparison of the differences between total period and period 1 (medians = 0.0 in the cetirizine group, 0.03 in the placebo group and -0.06 in the ketotifen group) was not significant (p = 0.249). See some details in Table XIII.

Median values of AGMED at baseline were 1.4 in the cetirizine group, 1.6 in the placebo group and 1.5 in the ketotifen group.
Global comparison of the differences between the total period and period 1 (medians = 0.0 in the cetirizine group, +0.17 in the placebo group and -0.01 in the ketotifen group) was statistically not significant (p = 0.281).
To be noticed a significant difference for the last period, in favour of ketotifen versus placebo (p = 0.019).
Some details are given in Table XIV, full details being reported in the statistical report.

Frequency of β₂-agonists and/or asthma medication use (FMED) decreased in the three groups during study. Baseline mean (median) FMED was 21.2% (10) in the cetirizine group, 28.2% (22.5) in the placebo group and 28.0% (23.1) in the ketotifen group.
For the total period, mean (median) FMED was 12.7% (8.3) in the cetirizine group, 25.6 (10.5) in the placebo group and 21.7 (10.1) in the ketotifen group.
Global comparison of the differences between total period and period 1 (medians = 0.0 in all groups) was statistically not significant (p = 0.860).
Some details are given in Table XV, full details in statistical report.

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5.3.6 Average index of severity of asthma (AGRAV, Table XVI)
Median values at baseline were 2.3 in the cetirizine group, 2.5 in the placebo group, 2.6 in the ketotifen group.
Global comparison of the differences between the total period and period 1 (medians = 0.00 in the cetirizine group, - 0.21 in the placebo group and - 0.01 in the ketotifen group) was not significant (p = 0.789).
For some details see Table XVI (full details in statistical report).

5.3.7 Lung function test at visits (FEV1)
Median values of FEV1 remained stable between the second and last visits in the cetirizine group: from 90.6 % to 89.8 %.
They improved slightly in the ketotifen group: from 84.1 % to 88.3 %, and somewhat more in the placebo group: from 87.5 % to 91.3 %.
These small differences are not statistically significant at V₆ (global comparison: p = 0.627).
To be noticed a nearly significant effect in favour of ketotifen at V₆ (global comparison p = 0.060).
Some details are given in Table XVII. Full details can be found in the statistical report.

5.3.8 Specific examination at visits (Table XVIII)
The number of patients with presence of wheezing, dyspnoea or cough at visit 1 and visit 2 together with the evolution at each visit compared to baseline = visit 2 (improvement/worsening) is given in Table XVIII.
No significant difference between groups were seen.
To be noticed a nearly significant effect in favour of ketotifen for cough at visit 3 (p = 0.058).

5.3.9 Evaluation of the quality of life
The evaluations made at visit 1 and visit 6, with a reference to the last 4 months were compared. To be noticed that about 50 % of the data is missing at V₆.
Improvements are observed from $V_1$ to $V_6$, but the medians of the differences ($V_6 - V_1$) are almost always $< 10$ mm on the scale. There is no treatment effect (see details in Table XIX).

5.3.10 Global evaluation of treatment

15/25 patients of the cetrizine group (60 %), 11/23 patients in the placebo group (48 %) and 20/37 patients in the ketotifen group (74 %) showed a good or excellent improvement after treatment. There is no statistically significant difference between the 3 treatment groups ($p = 0.193$). See details in Table XX.

5.4 Metacholine test

Only 16 patients underwent a PC20 measurement before and after treatment (4 in the cetrizine group and 6 in the placebo and in the ketotifen groups). The number of patients is too small to allow any valuable estimation of the possible treatment effect.

The same situation applies for PD20 measurements, where only 3 patients in the cetrizine group, 5 patients in the placebo group and 7 patients in the ketotifen group had measurements done at $V_2$ and at $V_6$.

Individual values are given in Table XXI.
6. Analysis of safety

6.1 Adverse events

6.1.1 Frequency of adverse events (Table XXII)

7/25 patients (28 %) reported a total of 9 adverse events in the cetirizine group
3/24 patients (12.5 %) reported a total of 3 adverse events in the placebo group
and 13/27 patients (48.1 %) reported a total of 21 adverse events in the ketotifen group.

The distributions of the numbers of adverse events reported are statistically
different in the 3 groups (p = 0.014) and being more frequent in the ketotifen group
than in the placebo group (p = 0.004). The differences between cetirizine and
placebo and between cetirizine and ketotifen were not statistically significant (p =
0.158 and 0.111 respectively).

See details in Table XXII.

6.1.2 Nature of adverse events (Table XXIII)

The most frequent adverse event in the cetirizine group was pharyngitis (2
patients); all other adverse events in the cetirizine group were reported only once.

In the placebo group, the 3 adverse events were reported only once.
In the ketotifen group, appetite increase and rhinitis were the most reported
adverse events (4 patients each), followed by headache and pharyngitis (3
patients each).

All adverse events mild or moderate, except one severe case of nervousness in
in the ketotifen group.

Concerning the relationship to the test drugs, answers were mainly "no" or
"possible". The only "yes" concerned the somnolence reported in the cetirizine
group.

No patient withdrew from the study because of an adverse event. No serious
adverse events were reported.

All details can be found in Table XXIII.
6.2 Laboratory results

6.2.1 General evaluation

In all patients, the two blood tests foreseen in the protocol were performed except for one patient in the ketotifen group and one patient in the placebo group who did not have the second series of tests (patients refused).

For neutrophils, lymphocytes, eosinophils, basophils, monocytes, total proteins SGOT and urea, 10 % to 20 % of patients have a missing result at least one laboratory.
6.2.2 Individual data

Careful review of the results of each patient, in particular for hepatic and renal tests, showed a few abnormalities.

The details of the laboratory tests results exceeding the norms by more than 10% are shown in Table XXV.

This was the case for 5 patients in the cetirizine group, 6 patients in the placebo group and 6 patients in the ketotifen group, but no clinically relevant abnormalities were observed.

7. Power a posteriori of the trial (see Table XXVI)

For the primary efficacy variables, the power achieved in this study (sample size about 25 patients per group, $\alpha$ error = 5%) is about 90% to detect a difference of 20% between therapy mean evolutions (total period - period 1).
IV. DISCUSSION

The patients included in this study improved in the 3 treatment groups, but the differences between treatments were globally not statistically significant.

Indeed, the very few statistically significant differences observed here and there (AGLN at period 3 in favour of cetirizine, AGMED at the 5th period in favour of ketotifen) have a very limited statistical relevance since the multiplicity of statistical tests implies that $p$ values need to be smaller than 5 % to indicate a significant result.

From a clinical point of view, the improvements observed in the 3 groups were poor. The differences between them were small and without any clinical relevance.

It must be underlined that the size of the treatment groups was rather small, so that differences between groups of less than 20 % for the FAST could not be detected as statistically significant. It is also important to note that the median room for improvement was rather low (from 27 % to 38 % for the FAST).

Thus, with a small room for improvement and a restricted sample size, it was almost impossible to observe statistically significant differences, unless almost complete cure was observed in one group and no improvement or aggravation was observed in another group. This is not the case here.
The analysis of safety shows that significantly more patients reported adverse events in the ketotifen group than in the placebo group. These results are to be balanced by the analysis of the so-called "side effects", i.e. any adverse events with a possible or established relationship to the test drug as reported by the investigator. Two side effects were observed in the cetirizine group (one appetite increase and one somnolence) and in the placebo group (one appetite increase and one loss of appetite), and six side effects were observed in the ketotifen group (four appetite increase, one somnolence and one nervousness). This side effect profile is completely in line with what has been reported previously with cetirizine and ketotifen in studies in asthma.
V. CONCLUSION
The results of this study showed neither clinical nor statistical significant differences between the efficacy of cetirizine (5 mg, 10 mg or 15 mg b.i.d. according to body weight), ketotifen (1 mg b.i.d.) and placebo.
Adverse events were more frequent in the ketotifen group than in the cetirizine group and placebo group.
VI. REFERENCES

1. GENGÓ FM, DABRONZO J, YURCHAK A, LOVE S, MILLER JK
   The relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine.

2. RIHOUX JP, DUPONT P
   Comparative study of the peripheral and central effects of terfenadine and cetirizine 2HCl.

3. MICHEL L, DE VOS C, RIHOUX JP, BURTIN E, BENVENISTE J, DUBERTRET L
   Inhibitory effect of oral cetirizine on in vivo antigen induced histamine and PAF-acether release
   and eosinophil recruitment in human skin.

4. GHOSH SK, DE VOS C, PATEL KR
   Effect of cetirizine on histamine and LTD4-induced bronchoconstriction in patients with atopc
   asthma.

5. WASSERFALLEN JB, LEUENBERGER PH, PECOUD A
   Effect of cetirizine on the early and late allergic reactions in a bronchial provocation test (BPT).
   XIVth International Congress of Allergy and Clinical Immunology, Kyoto, 13-18 October 1991.

6. REDIER H et al
   Cetirizine inhibits bronchial eosinophil recruitment induced by allergen inhalation challenge in
   allergic asthmatics.
   XIVth International Congress of Allergy and Clinical Immunology, Kyoto, 13-18 October 1991.

7. Internal report - CE90C1901
   Multicentre, double blind study in three parallel groups to compare two doses of cetirizine (10 or
   15 mg 2x/day) with placebo over three months in the treatment of atopic perennial asthma in
   patients aged 12 years and over.

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REFERENCES (continued)

8. Internal report - CE89F151
A 3 month, randomised, double blind study to compare the safety and efficacy of cetirizine 2HCl, (10 or 15 mg tablets bd for 12 weeks) and placebo in the treatment of patients with perennial atopic asthma currently treated with inhaled corticosteroids and $\beta_2$-mimetics on request.

9. Internal report - RRCE91L1901
A double-blind multicentre study of 3 parallel groups comparing the efficacy and safety of cetirizine (1/2, 1 or 1 1/2 10 mg tablet b.i.d. according to body weight), cromoglycate (20 mg inhalation capsule q.i.d) and placebo in the treatment of perennial allergic asthma in children and adolescents.

A candian multicenter study with Zaditen (ketotifen) in the treatment of bronchial asthma in children aged 5 to 17 years.

A multicenter trial of the prophylactic effect of ketotifen, theophylline, and placebo in atopic asthma.

12. LOFTUS BG, PRICE JF
Long-term, placebo-controlled trial of ketotifen in the management of preschool children with asthma.

13. VOLOVITZ B, VARSANO I, CUMELLA JC, JABER L
Efficacy and safety of ketotifen in young children with asthma.