Synopsis of study report: 198/2003
Location in Module 5:

Study Code:
BY9010/M1-125

Report Version:
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Title of the study:

A 3-period double-blind, crossover study on the onset of action of inhaled ciclesonide (7 days of 400 µg sid versus 800 µg bid versus placebo) on airway responsiveness to adenosine monophosphate (AMP), sputum eosinophils and exhaled breath nitric oxide (NO) in patients with asthma

Principal Investigator:

Study center:

One study center: London SW3 6HP, United Kingdom (UK)

Publication (reference): Not applicable

Studied period (years): 21 May 2002 – 13 May 2003

Clinical phase: III

Objectives:

The aim of the present 3-period crossover study was to investigate, in patients with asthma, the onset of action of two doses of ciclesonide (400 µg/day i.e.400 µg sid and 1600 µg/day i.e. 800 µg bid) with respect to airway hyperresponsiveness to AMP, exhaled nitric oxide (NO), and changes in other markers of airway inflammation. In addition, the study was to provide information on the safety and tolerability of ciclesonide.

Methodology:

The present study had a double-blind, placebo-controlled, 3-period crossover design. It consisted of a baseline period (visit B0) followed by 3 treatment periods (TI, TII, TIII). The treatment periods lasted 7 days and were separated by a washout period of 4-6 weeks. Patients were randomized to one of six treatment sequences and received either ciclesonide 400 µg sid, ciclesonide 800 µg bid, and placebo according to the allocated sequence.

Within each treatment period patients came to the investigational site at Day 1, Day 3, and Day 7 of treatment (visits T0, T1, and T2 in period TI; visits T3, T4, and T5 in period TII; visits T6, T7, and T8 in period TIII). At all study visits, patients underwent the following examinations in a sequential order: measurement of exhaled NO (2 hours after inhalation of study medication), lung function test (2 hours and 5 min post-inhalation), AMP challenge (2 hours and 30 min post-inhalation), induction of sputum (4 hours post-inhalation).

Adverse events were documented by the investigator throughout the study. The laboratory values were determined at baseline (visit B0) and at the end of each treatment period (visits T2, T5, and T8). ECG recordings were made at visit B0. Physical examination including vital signs (blood pressure and heart rate) were performed at the start and the end of the study (visits B0 and T8).

No. of subjects (total and for each treatment):

In total, 25 patients were enrolled in this monocenter study. The full analysis set consisted of 21 randomized patients who had taken at least one dose of study medication. The valid cases set consisted of 17 patients.

Diagnosis and criteria for inclusion:

For inclusion in the study patients had to be in good health with the exception of asthma and they met the following criteria:

- Written informed consent
- Age: 18 - 45 years
- History of atopic disease
- Perennial bronchial asthma for ≥ 6 months as defined by ATS criteria
- Currently using only inhaled short acting ß2-agonists as required (for at least 4 weeks prior to baseline period B0)
- Stable asthma, i.e. no exacerbation or relevant respiratory tract infection within 2 months prior to study entry
- FEV_1 ≥ 70% predicted as measured at least 8 hours after the last use of the rescue medication
- Hyperreactivity to AMP ($PC_{20}FEV_1$ < 25 mg/ml)

- Who, with the exception of asthma, are in good health
- Non-smokers as well as ex-smokers with either ≤ 10 pack-years or more than 6 months of smoking abstinence

In addition, for entry into the next treatment period (i.e. TII after visit W1 and TIII after visit W2), the hyperresponsiveness of patients to AMP as indicated by their $PC_{20}FEV_1$ had to be in the same range as that observed at visit B0 (i.e. ± two doubling concentrations of the value).

Test product:

- Low dose treatment: ciclesonide 100 µg/puff ex-valve (corresponds to 80 µg/puff ex-actuator);
- High dose treatment: ciclesonide 200 µg/puff ex-valve (corresponds to 160 µg/puff ex-actuator).

Dose and mode of administration:

- Low dose treatment (ciclesonide 400 µg/day): 4 x 100 µg ciclesonide/puff in the morning and 4 puffs placebo in the evening;
- High dose treatment (ciclesonide 1600 µg/day): 4 x 200 µg ciclesonide/puff in the morning and in the evening.

Batch No.:

- MDI for low dose of ciclesonide treatment: batch No. 2BGA001
- MDI for high dose of ciclesonide treatment: batch No. 4BGA001

Duration of treatment:

Three treatment periods, each lasting 7 days.

Reference product:

Placebo

Dose and mode of administration:

Placebo: 4 puffs in the morning and 4 puffs in the evening.

Batch No.:

Placebo inhaler: batch No. 0BG003

Criteria for evaluation:

Primary efficacy variable: provocative concentration leading to a 20% decrease in the forced expiratory volume in one second ($PC_{20}FEV_1$) during an AMP challenge.

Secondary efficacy variables: FEV_1 from spirometry, exhaled NO, inflammatory markers in induced sputum (eosinophils, basophils, mast cells).

Secondary safety variables: laboratory values, physical examination, vital signs, adverse events.

Statistical methods:

According to the a priori ordered hypotheses, ciclesonide 800 µg bid was first tested for superiority over placebo with regard to the post-treatment/pre-dose ratio of $PC_{20}FEV_1$; this was performed in a stepwise manner on Day 7, Day 3, and then Day 1 of treatment. If this was confirmed, the testing procedure continued by testing ciclesonide 400 µg sid for superiority over placebo, in a stepwise manner, on Day 7, Day 3, and then Day 1 of treatment. If superiority was once more demonstrated, a subsequent test for superiority of ciclesonide 800 µg to ciclesonide 400 µg sid was performed, in this case, starting on Day 1 and then Day 3 and Day 7 of treatment. The ITT-analysis was stipulated as the primary analysis for the primary variable $PC_{20}FEV_1$ (AMP challenge).

$PC_{20}FEV_1$, was calculated before and after the intake of study medication within each treatment period (at Day 1, Day 3 and Day 7). A log concentration-response curve was constructed and the concentration of the provoking agent that caused a 20% fall in FEV_1 was calculated by (log-)linear interpolation considering the concentration that led to a fall in FEV_1 of more or equal than 20% (threshold concentration).

The primary variable was analyzed by means of an analysis of variance (ANOVA) on the log-transformed ratio of $PC_{20}FEV_1$ at endpoint vs baseline. In addition to hypothesis testing, least squares (LS) means of the PC_{20} ratios and two-sided 95%-confidence intervals were presented by day for the differences between treatments. Within-treatment ratios were reported by treatment and day using geometric means and the 95%-confidence limits.

The secondary variables FEV_1 from spirometry, NO exhalation and eosinophils from sputum were analyzed in an exploratory manner. An analysis of covariance (ANCOVA) was performed to analyze FEV_1 (based on the difference in FEV_1 between endpoint and baseline). The ANCOVA model included the baseline value as covariate and treatment, treatment period as well as 'patient within sequence' as factors. Between-treatment differences of exhalation of NO and sputum variables were compared between treatments by means of Pratt's

modification of the Wilcoxon's signed-rank test. All other secondary variables were analyzed in a descriptive manner.

SUMMARY - CONCLUSIONS

Efficacy results:

In contrast to placebo, both doses of ciclesonide (400 µg sid and 800 µg bid) inhaled within a 7-day treatment period resulted in a statistically significant improvement of $PC_{20}FEV_1$ during an AMP challenge. On Day 7, the increase in $PC_{20}FEV_1$ amounted to 30.61 mg/mL for ciclesonide 400 µg sid and 33.02 mg/mL for ciclesonide 800 µg bid.

The decrease in airway hyperresponsiveness to AMP observed in patients treated with ciclesonide already occurred on Day 1 (i.e. within 2.5 hours after inhalation of the first dose). Superiority of ciclesonide over placebo with respect to the primary variable $PC_{20}FEV_1$ could be shown for both doses of ciclesonide.

Among the secondary efficacy variables, an improvement in FEV_1 was observed after 3 and 7 days of treatment with 400 µg sid or 800 µg bid, but not after placebo. Superiority of ciclesonide over placebo could be demonstrated for the higher dose after 3 days treatment, and for both doses after 7 days treatment. Exhaled NO levels decreased after the 7-day treatment period in patients treated with ciclesonide (400 µg sid or 800 µg bid). Superiority of ciclesonide over placebo with respect to exhaled NO was shown for both doses of ciclesonide already after 3 days treatment.

Exploratory analysis of sputum samples revealed a decrease in the percentage of eosinophils after a 7-day treatment with ciclesonide; the decrease in eosinophils was more pronounced for the higher dose of ciclesonide 800 µg bid. Between-treatment differences did not reach statistical significance. As the percentage of eosinophils at the beginning of the treatment periods was generally low in this study, there was not much room for improvement with respect to sputum variables.

Safety results:

During the treatment periods, a total of 37 AEs were experienced by 16 patients. In total, 33.3% of the patients experienced at least one AE during the ciclesonide 400 µg sid treatment period, 61.9% of patients during the ciclesonide 800 µg bid treatment period, and 25% of patients during the placebo treatment period. Most of the AEs experienced during treatment were mild or moderate in intensity and were assessed by the investigator as unrelated or unlikely related to the study medication.

The most frequently reported AEs in this study affected the respiratory system and included pharyngitis, nasopharyngitis, and cough. AEs frequently reported for other system organ classes were headache and chest pain. Considering the small number of patients and the causality assessments, no safety concern can be derived from these data.

No death occurred in the present study. Neither SAEs nor AEs leading to study discontinuation were reported.

Laboratory investigations, physical examination, and vital signs (blood pressure and heart rate) did not disclose any influence of the study medication.

Conclusion: