Rhinocort® (budesonide) Aqua Nasal Spray

RHINOCORT AQUA 05-3039
STUDY SYNOPSIS

PRODUCT:
Rhinocort (budesonide) Aqua

STUDY TITLE:
A DOUBLE-BLIND COMPARISON OF FOUR DOSES OF RHINOCORT® AQUA PUMP SPRAY (BUDESONIDE) AND PLACEBO IN THE TREATMENT OF ADULTS AND CHILDREN WITH PERENNIAL ALLERGIC RHINITIS

PROJECT NUMBER: 850-43
STUDY NUMBER: 05-3039
REPORT NUMBER: 05-CR-3039
STUDY DESIGN: Double-Blind, Placebo-Controlled, Parallel groups
RANDOMIZATION PROCEDURE: Randomized, Stratified based upon patient’s age
DOSAGE REGIMEN AND GALENICAL:
Patients were treated with either Rhinocort® (budesonide) Aqua 32 µg, 64 µg, 128 µg or 256 µg or matched placebo

PATIENT POPULATION:
Adult patients ages 18 and above
Pediatric patients between the ages of 6 to 17

NUMBER OF PATIENTS: 478 (450 planned)
NUMBER OF CENTERS: 20 centers throughout the United States
DURATION OF TRIAL: 1 week run-in followed by 6 weeks of treatment
TIMELINE: December 1994 to April 1995

PATIENT SELECTION -demographics
478 patients were randomized. 245 males and 233 females were included in the study. 447 patients completed the study. 11 patients discontinued prior to completion due to adverse events.
Rhinocort® (budesonide) Aqua Nasal Spray

-inclusion criteria:

1. Males or females aged six years or older.
2. A clinical diagnosis of perennial allergic rhinitis for at least the previous two years. Symptoms from the previous year should have been at least moderately severe and should have required treatment. Patients who had only used decongestants were not to be permitted.
3. The presence of perennial allergen sensitivity was to be verified by a positive Multi-Tes® skin test (3 mm or greater than the negative control) documented at the time of screening. NOTE: If using an intradermal test to confirm a response, a positive response was defined as 5 mm greater than the negative control.
4. Two of the three nasal symptoms (i.e., blocked nose, runny nose, or sneezing) must have had a score of two or higher for any four out of the last seven days during the baseline period.
5. Willingness to participate as indicated by signed informed consent. For patients who were under the legal age of majority (i.e. minors), both the legal guardian and the patient (if possible) must have given their signed informed consent.

-exclusion criteria:

1. Significant diseases of the cardiovascular, respiratory, hepatic, gastrointestinal, renal, neurological, musculoskeletal, endocrine, or metabolic systems (e.g. diabetes mellitus, hepatitis, uncontrolled hypertension or hypertension requiring more than two drugs to achieve control) or other gross physical impairment or any history of convulsive disorder as judged by the investigator.
2. History of carcinoma (excluding basal cell carcinoma) in the past five years.
3. A history of psychosis or poor motivation that are likely to limit the validity of consent to participate in the study.
4. Patients with a planned hospitalization during the study.
5. Clinically relevant baseline laboratory results which defined a disease or condition which, in the opinion of the investigator, would either put the patient at risk because of
participation in the study or could influence the results of the study, or the patient's ability to participate in the study.

6. Women who were pregnant or nursing. Female patients of childbearing potential (after first menstrual period) must have been surgically sterile or using medically accepted contraceptive measures. If the patient is naturally post-menopausal she must not have had a menstrual period within 24 months prior to entry into the study. All female patients of childbearing potential, must have a negative serum pregnancy test at Visit 1.

7. Patients who have been recently exposed (or are at risk of being exposed) to chicken pox or measles.

8. Patients with known hypersensitivity to budesonide.

9. Structural abnormalities of the nose (e.g. septal deviation, nasal polyps) symptomatic enough to cause significant nasal obstruction as judged by the investigator.

10. Active diseases of the nose including: Infectious rhinitis, Sinusitis, Rhinitis medicamentosa and Atrophic rhinitis.

11. Seasonal allergic rhinitis. Patients with coexisting seasonal allergic rhinitis may be included providing the specific seasonal allergen is not in season.

12. Any upper respiratory tract infection three weeks prior to Visit 1.

13. Topical nasal glucocorticosteroid treatment within one month prior to Visit 1.

14. Patients on immunotherapy for perennial allergens for less than six months, or who are not on stable maintenance doses.

15. Use of short-acting or long-acting antihistamines, topical or oral decongestants, or other medications which could mask the symptoms of rhinitis (i.e., tricyclic anti-depressants, major tranquilizers or anti-epileptic agents) within three days of enrollment (Visit 1).

NOTE: Seldane® (terfenadine) must be discontinued two days, Claritin® (loratadine) four days and Hismanal® (astemizole) must be discontinued 12 weeks before Visit 1.

16. Use of nasal cromolyn sodium or nedocromil within two weeks prior to Visit 1. Note: This exclusion also applies to patients using nebulized cromolyn sodium via face mask.
Rhinocort® (budesonide) Aqua Nasal Spray

17. Systemic glucocorticosteroid therapy for any reason in the one month prior to Visit 1.
18. Asthma requiring treatment with systemic glucocorticosteroids.
19. A history of drug or alcohol abuse within the past five years.
20. An infirmity, disability or geographical location which seems likely to prevent regular attendance for patient visits.
21. Treatment with an investigational drug in the previous 30 days.
22. Previous randomization into the study.

Duration of Disease: Perennial Allergic Rhinitis, 14.9 years (mean)

Breakthrough Medication: None

INVESTIGATIONAL METHODS

-Assessments:
1) Skin Tests (Multi-Test®)
2) Medical History
3) Physical Examination
4) Nasal Examination
5) Nasal Cytology (Rhinoprobe™)
6) Laboratory Assessments
7) Serum and Urine pregnancy tests on all females of childbearing potential
8) Quality of Life Questionnaire

-Efficacy:
Patients kept a daily symptom diary where they assessed their nasal symptoms during a 24 hour period.

-Statistical analysis:
The primary efficacy variable was nasal index score (NIS), calculated as the sum of individual scores (scale 0-3) for three nasal symptoms (congestion, runny nose, and sneezing). Active treatments were compared to placebo in terms of change in NIS from baseline to NIS average over the Six-week treatment period.

The secondary efficacy variables included individual nasal symptoms (congestion, runny nose, and sneezing), patients overall
assessment of treatment efficacy, and discontinuations from the study.

RESULTS

-Efficacy

In the overall analysis, nasal index scores decreased significantly from baseline for active treatments 32μg, 64 μg, and 256 μg compared to placebo. Although the mean decrease in NIS from baseline in the 128μg treatment group compared to placebo was similar to mean decreased in the other active treatment groups, the difference in mean change in NIS from baseline between 128μg and placebo marginally failed to reach significance. Analyses comparing treatments for each age group were also performed. However, since this study was specifically designed to analyze efficacy endpoints combining all patients, the results of these subanalyses were used to explore treatment differences within each age group. In both age groups, nasal index scores decreased from baseline for all treatment groups. In the adult group, decreases in NIS from baseline for all active treatments compared to placebo were significantly greater. In the pediatric group, although all active treatments resulted in decreases in NIS from baseline, the differences in mean change in NIS from baseline between active treatments and placebo were not significant. NIS for the highest active dose (256 μg) was compared to the lowest dose (32 μg) overall and within each age group. No significant differences could be demonstrated between 256μg and 32 μg in terms of change in NIS from baseline overall or within each age group.

In the overall analyses of individual nasal symptom scores, congestion was significantly reduced in all four treatment groups compared to placebo, and runny nose and sneezing were significantly reduced in both the 32μg and 256 μg treatment groups compared to placebo. In the adult group, congestion was significantly reduced for all four active treatments compared to placebo, and sneezing and runny nose were significantly reduced for active treatments 32 μg, 128 μg, and 256 μg compared to placebo. In the pediatric group, no significant differences between active treatment and placebo were observed in terms of changes in
individual nasal symptom scores from baseline. Patient’s overall assessment of treatment efficacy indicated that each active treatment resulted in significantly greater control over symptoms compared to placebo as measured by overall assessment scores. Mean overall assessment scores, adjusted for center, ranged from 2.27 to 2.33 for all active treatments, and adjusted mean overall assessment score in the placebo group was 1.98. The results comparing overall assessment scores within the adult group indicated a similar result as in the overall analysis. In the pediatric group, mean overall assessment scores were higher for each active treatment compared to placebo, with significance being achieved for the 128 µg treatment group.

The analysis of nasal cytology resulted in significantly greater decreases in eosinophils and basophilic cells for all active treatments compared to placebo in the overall analysis. Mean scores for eosinophils decreased for all active treatments, with adjusted mean changes ranging from -0.42 to -0.62, while there was no mean change for placebo. In the adult group, eosinophils decreased for all active treatments, but the differences for active treatment compared to placebo were not significant. In the pediatric group, decreases in eosinophils were significantly greater for all active treatments compared to placebo. In the overall analysis, basophil scores decreased for all active treatments, with adjusted mean changes ranging from -0.17 to -0.39, while the adjusted mean change for placebo was 0.30. Basophils decreased significantly for all active treatments compared to placebo in both the pediatric and adult groups, although there appeared to be a slightly better response in the pediatric group than in the adult group. No differences between all active treatments and placebo were observed for neutrophils.

The analysis of Quality of Life demonstrated some improvement in symptoms within all treatment groups, including an observed placebo effect. In the adult group, there were some significant improvements for active treatments compared to placebo. All active treatments showed significant improvement in “practical problems” compared to placebo. Scores for “activities” and overall Quality of Life scores significantly decreased for 32µg and 256 µg compared to placebo, and decreases in “sleep” and “non-hayfever symptoms” scores were greater for the 256 µg group compared to
Rhinocort® (budesonide) Aqua Nasal Spray

placebo. Scores for “nasal symptoms” also decreased for all active treatments; this result was also reflected in the results of the analyses of NIS and individual nasal symptom scores. In children (6-11 years) and adolescents (12-17 years), decreases in scores within each domain and overall were not significantly greater for any of the active treatments compared to placebo. A total of 236 patients reported one or more adverse events, 186 (49%) in the Rhinocort treatment group and 50 (52%) in the placebo group. The four most commonly reported adverse events were respiratory infection (12% Rhinocort, 16% placebo), pharyngitis (7% Rhinocort, 4% placebo), epistaxis (8% Rhinocort, 2% placebo), and headache (7% Rhinocort, 11% placebo). The majority of the adverse events were of mild or moderate intensity. There were no apparent differences in the distribution of adverse events across treatment groups. No serious adverse events were reported.

Of the 478 patients randomized into the study, 11 patients (2%) were discontinued due to adverse events. None of these events were serious. No apparent differences in the rates of discontinuation due to adverse events were observed across treatment groups.

-Laboratory Assessments

Laboratory safety tests (Clinical Chemistry, Hematology, and Urinalysis) and a serum pregnancy test (for female patients of childbearing potential) were performed at visits 1 and 5. In addition, urine pregnancy tests were performed at interim visits (visits 2 to 4). No clinically relevant trends or shifts were observed in changes over the course of the study.

CONCLUSIONS

This study demonstrated that Rhinocort Aqua is effective and well-tolerated in pediatric and adult patients with perennial allergic rhinitis. Thereby, we suggest an appropriate dose range of Rhinocort Aqua in this population. This is in line with the recommendation of the initial treatment with 256 μg and a down titration to the lowest effective therapeutic dose on an individual basis.

Camilla Schrewelius, Astra Draco Coordinator

Date 971014