AstraZeneca

SD-008-3037

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Budesonide CIR capsules

ACTIVE INGREDIENT: Budesonide

Trial title (number): Efficacy and Safety of Budesonide CIR versus Prednisolone in Children with Active Crohn's Disease

Developmental phase:IIIA
First subject recruited:24 April 1998
Last subject recruited:22 December 2000
Approval date: 23 April 2001

OBJECTIVES

The primary objective of the study was to evaluate the efficacy of budesonide CIR compared with prednisolone in children with active CD with respect to remission after 8 weeks' treatment.

A secondary objective was safety measured as adrenal function, morning plasma cortisollevels and frequency of possible glucocorticosteroid side effects.

METHODS

STUDY DESIGN
The study was a randomized, double-blind, double-dummy, active-controlled multi-centre trial, using a parallel group design, stratified for pubertal development.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION
The diagnosis was active Crohn's disease, defined by a Crohn's Disease Activity Index(CDAI)≥200 units, limited to the ileum, ileo-caecal region and/or ascending colon apartfrom scattered apthous ulcers elsewhere.

The main inclusion criteria

Both out and hospitalized patients of either sex could be included if they:

- Were 6-16 years old and had not passed their 17th birthday (50% of the patients being prepubertal; Tanner stage≤II).
- Had an active disease as specified by the diagnosis.
- Were able to swallow capsules.
- Gave their verbal informed assent or consent to participate in the study and at least one of their parents, or a legal guardian, gave his/her written informed consent before any study related procedures were conducted.

The main exclusion criteria

Patients were excluded from the study if they:

- Were pregnant or breast-feeding or did not use acceptable contraceptives, as judged by the investigator.
- Had >50 cm of the small bowel resected or any resection of the proximal colon extending beyond the mid-transverse colon.
- Had active CD of the distal colon verified with an investigation of at least the most distal 25 cm using either rigid or exible igmoidoscopy/colonoscopy anytime during the 8 weeks prior to or at Visit 1.
- Had a body weight <20 kg.
- Had signs of septic complications, abscess, mechanical obstruction, perforation or anactive fistula (with the exception of chronic asymptomatic anorectal fistula).
- Were scheduled to undergo in-patient surgery during the study.
- Were on total parenteral nutrition or chemically defined, nutritionally complete, aminoacid-based, polymeric peptide-based or modular diets 7 days before Visit 1.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

The test product was budesonide CIR capsules and the mode of administration was 9 mg once daily for 8 weeks taken orally as 3 capsules of 3 mg each followed by 6 mg once daily for 4 weeks taken orally as 2 capsules of 3 mg each.

Batch numbers used were: AD 1169, YM 1057, YM 1060, and ZL 1128.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

The comparator product was prednisolone tablets, 2.5 mg, 5 mg and 10 mg, and the mode of administration was orally once daily according to the following dosing scheme:

Week	1-4	5	6	7	8	9	10	11	12
Body weight	**Prednisolone dose (mg)**								
≤25 kg	20	17.5	15	12.5	10	7.5	5	2.5	2.5
>25-≤30 kg	25	20	15	12.5	10	7.5	5	2.5	2.5
>30-≤35 kg	30	25	20	15	12.5	10	7.5	5	2.5
>35-≤40 kg	35	30	25	20	15	10	7.5	5	2.5
>40 kg	40	35	30	25	20	15	10	5	2.5

Batch numbers used were:

Prednisolone tablet	**Batch number**
2.5 mg	DYB 61, DAG 62
5 mg	DXA 4, DAH 5
10 mg	DYB 32, DZK 33

In addition to the active drugs placebo budesonide CIR capsules from batch number ZA405, AD 406, and AL 407, and placebo prednisolone tablets from batch number DYL 104 were used in the study.

Additional product: EMLA®patch, a topical anasthetic patch was used before bloodsamplings. The anasthetic consists of lidocaine 25 mg, prilocaine 25 mg, polyoxyethylenericinol hydrogenate, carboxypolymethylene and natrium hydroxide. Patches from batchnumber ZB 2074 and ZI 2125 were used in the study.

DURATION OF TREATMENT

The duration of treatment was 12 weeks

MAIN VARIABLE(S):

- EFFICACY

The primary efficacy variable was remission where remission is defined as a CDAI of≤150 units.

- SAFETY

The safety variables measured were adrenal function, morning plasma cortisol levels,frequency of possible glucocorticosteroid side-effects and adverse events.

STATISTICAL METHODS

Chi-square tests were used to compare proportions. Quantitative variables were analyzed by analysis of variance, t-tests and Wilcoxon-tests. All tests were two-sided. P-values notexceeding 5% are considered significant. The outcome after 2, 4, 8 and 12 weeks wereevaluated, but 8 weeks was considered the primary time-point.

PATIENTS

A total of 120 children (60 prepubertal and 60 pubertal) between 6-16 years, male andfemale with active CD (CDAI≥200) affecting the ileum and/or ascending colon wereplanned to be randomized in the study. However, due to the decision to terminate the study prematurely only 48 children were randomized.

	Budesonide	**Prednisolone**	**Total**
No. planned	60	60	120
No. randomized and treated	22	26	48
Males/Females	15/7	18/8	33/15
Mean age (range)	13 (8-16)	13 (8-16)	13 (8-16)
Tanner stage≤2	12	13	25
Tanner stage >2	10	13	23
Baseline value CDAI (range)	239 (182-307)	268 (145-411)	255 (145-411)
Baseline value PCDAI (range)	39 (15-58)	45 (28-65)	42 (15-65)
No. analysed for efficacy	22	26	48
No. analysed for safety	22	26	48
No. completed	14	16	30

Results:

- EFFICACY RESULTS

Within two weeks 50% of the patients had gone into remission in with both budesonide and prednisolone. During the rest of the study, the percentage of patients in remission in the budesonide group remained at a level just above 50%. This was seen even when the dose was reduced from 9 mg to 6 mg during the last 4-week period. In the prednisolone group, the percentage of patients in remission showed a continued increase over the four weeks when the initial, highest dose of the drug was given. During the subsequent four weeks when the prednisolone dose was gradually reduced to approximately half the initial dose, the fraction of children in remission remained at about the same level. However, when the prednisolone dose was further reduced, the percentage of children in remission started to decline. The difference in percentage of patients in remission after 8 weeks, though numerically quite large, 55% for budesonide vs. 71% for prednisolone, is not statistically significant. It can therefore not be ruled out that the two treatments are equivalent with respect to percentage of patients in remission, but due to the small size of the two treatment groups the uncertainty in the conclusion (the risk of a type II error) is considerable. With this reservation, the present data suggest that with the dosing regimen used in the present study, there was transiently a somewhat higher efficacy with prednisolone than with budesonide, a difference that disappeared when the dose was tapered.

- SAFETY RESULTS

Prednisolone had a considerably stronger suppressing effect than budesonide on the HPA-axis. During the initial four weeks of the trial, when the highest dose of prednisolone was given, only 10% of the children had plasma cortisol of at least 150 nmol/L (the lower normal limit). The corresponding percentages during the 8-week period when budesonide 9 mg was given varied between 37% and 58%. The difference in percentage of patients with an abnormal function as

response to the ACTH test (which might be considered the most important of the secondary variables from a safety point of view) shows a close to statistically significant superiority for budesonide (P=0.07). The difference in percentage of patients with abnormal morning P-cortisol was also close to significant (P=0.052). The quantitative difference in morning P-cortisol was highly significant in favour of budesonide (P=0.0028). In agreement with the effect on the HPA-axis, hypercorticism, particularly appearing as moon-face or acne, was considerably more frequent among the prednisolone treated children. Second to endocrine disorders, gastrointestinal AEs (mainly caused by the underlying disease) were most common in the two treatment groups. Beside relatively strong suppression of the HPA-axis function, particularly with prednisolone, the present data have not revealed any findings in children that were not known from studies in adults with Crohn's disease.

Reference:

Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. 17 July 2003. Johanna C. Escher and the european Collaborative Researcg Group on Budesonide in Paediatric IBD. European Journal of Gastroenterology & Hepatology 2004, 16:47-54

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Entocort™ (budesonide), Healthcare Professionals should view their specific country information.