AstraZeneca

08-3039

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Entocort®, capsules

ACTIVE INGREDIENT: Budesonide

Trial title (number): Effect of treatment with budesonide CIR capsules and prednisolone on bone density, bone metabolism and osteoporosis in subjects with Crohn's disease, measured using dual energy X-ray absorptiometry (MATRIX).

Developmental phase: IIIB
First subject recruited: 03 July 1996
Last subject recruited: 31 May 2001
Approval date: 21 August 2002

OBJECTIVES

The primary objective was to compare the influence of treatment with budesonide or prednisolone on BMD in subjects with Crohn's disease affecting the ileum and/or the ascending colon, using dual energy X-ray absorptiometry (DXA).

Secondary objectives were to compare the following variables: remission rate, defined as a Crohn's disease activity index (CDAI) equal to or less than 150 (17), number of incident fractures, change in markers of bone metabolism, accumulated drug intake, health-related quality of life, and direct health care costs and indirect costs of loss of production due to Crohn's disease.

METHODS

STUDY DESIGN

This was an open (blinded only for the person examining the radiographs and to the Quality Assurance Centre, Synarc Inc., former Hologic MDM), randomised study with parallel groups. Both steroid-dependent and steroid-free subjects were recruited.
1) Steroid-dependent subjects were defined as having received glucocorticosteroids for at least 4 out of 6 months immediately prior to visit 1. For these subjects to be eligible, they also had to have a prednisolone/prednisone intake of 7-20 mg daily and had a CDAI ≤ 200 at randomisation.
2) Steroid-free subjects, at visit 1, were defined as having received no glucocorticosteroids during the 6 months immediately prior to visit 1. These subjects had to have a CDAI > 150 at randomisation.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

The studied indication was Crohn's disease affecting the ileum and/or the ascending colon.

Inclusion criteria:

Both hospitalized and out-subjects of either sex could be recruited if they:

- were between 20 and 70 years of age
- had the diagnosis of Crohn's disease verified by X-ray (small bowel follow-through) and/or endoscopy and histology
- had the disease localized only to the distal ileum, the ileo-caecal region and/or the ascending colon, except for scattered aphthous ulcers in the colon and rectum, assessed by colonoscopy or X-ray (small bowel follow-through as well as a barium enema) within 24 months prior to visit 1.

For steroid-dependent subjects to be randomised at visit 2 the following criterion had to be fulfilled:

- a disease activity defined as a CDAI $\leq$ 200.

For steroid-free subjects to be randomised at visit 2 the following criterion had to be fulfilled:

- a disease activity defined as a CDAI > 150.

Exclusion criteria:

Subjects were not eligible for this study if they:

- had undergone previous gastric surgery, except for closure of a perforation or selective vagotomy
- had > 100 cm of ileum resected, or any resection distal to the mid-transverse colon
- had an ileostomy, pouch or colostomy
- had disease proximal to the ileum
- had active Crohn's disease in the rectum verified by rigid (rectoscopy) or exible sigmoidoscopy within two weeks prior to visit 1
- had more than three spinal fractures during his/her life-time.

Furthermore steroid-free subjects were not eligible for this study if they:

- had received any glucocorticosteroids (excluding steroids for birth control, eye drops and low potency steroid ointments, e.g. hydrocortisone derivatives) at any time during the six months prior to visit 1.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide CIR capsules (Entocort ® capsules), 3 mg, manufactured by AstraZeneca Pharmaceutical Production, Södertälje, Sweden, were used in this study. The gelatin capsule contains acid-stable granules approximately 1 mm in diameter. Batch no:s: AE 1177, VK 517, XK 558, XK 561, XM 569, YB 571, YD 1035, YK 1049, ZB 1072, ZH 1110, ZH 1103 and ZL 1128. Budesonide $\leq$ 9 mg q.d.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Prednisolone tablets, 1 mg and 5 mg, manufactured by AstraZeneca R&D, Lund, Sweden. Batch no:s 1 mg: DXA 1 and DYE 2. Batch no:s 5 mg: DAH 5 and DXA 4. Prednisolone $\leq$ 40 mg q.d.

DURATION OF TREATMENT

Following a one-week run-in period, subjects within each category were randomly assigned to receive either budesonide (≤ 9 mg once daily) or prednisolone (≤ 40 mg once daily) for 2 years with the dose adjusted according to disease activity. The follow-up visits were carried out at 4 weeks ± 2 days, 3 months ± 1 week, 6 months ± 1 week, 12 months ± 2 weeks, 18 months ± 2 weeks and 24 months ± 2 weeks. Extra, unscheduled visits or contacts by telephone were required between the scheduled visits when a dose of either budesonide or prednisolone was adjusted.

MAIN VARIABLE(S):

- EFFICACY

Z-score of PA (Posterior Anterior) spine, which is computed from the bone mineral density (BMD) as Z=(BMD-M)/SD, where M and SD are the mean and standard deviation of BMD for normal subjects with the same sex and age.

- SAFETY

Incidence of adverse events and incidence of glucocorticosteroid side-effects

STATISTICAL METHODS

The primary analysis of efficacy is on intent-to-treat basis (ITT) and applies the last value extended principle (LVE) from the first on-treatment visit (Visit 3). Subjects are included in the ITT analysis if they took at least one dose of the study medication and have data on at least one follow-up visit.

The primary comparison of the two treatment groups is with respect to the changes in Z-score. The primary time-point is after 24 months. However, the groups will also be compared at all other visits as well as with respect to proportion of subjects in remission (CDAI ≤ 150), number of incident fractures, change in markers of bone metabolism and accumulated drug intake, and with respect to BMD itself and all other assessed variables.

For BMD, T- and Z-score, linear regression on time will be performed as an alternative analysis. Since a steeper decline in BMD is expected during the first six months in steroid-free subjects, separate analyses will be made for the first six months (Visit 2 to Visit 5) and for the time after six months (Visit 5 to Visit 8) in addition to an analysis for the whole time.

Linear regression on time is not planned for any other variables in the study.

The study protocol does not specify any analysis of hip and whole body measurements with DXA. The hip and whole body BMDs are analysed as secondary variables. Since there is less documentation about conversion of results between machines for these measurements, and about any kind of T- or Z-scores, the analysis is performed on the BMD values as reported, but with a statistical model that uses machine type as a factor.

DXA measurements performed more than two weeks after withdrawal from the study have been ignored, but all other BMD data have been used and allocated to the nearest of the scheduled timepoint, whenever data is analysed per visit. In the regression analyses the actual times have been used.

Separate analyses were planned and have been made for the two strata of subjects (STD and STF). Moreover, the STF stratum has been divided into two substrata: steroid-naïve subjects, who never had used oral steroids (STN), and currently steroid-free subjects, who had used oral steroids previously but not during the last six months (STP); this was decided at the analysis meeting with the steering committee before clean file, since this was found that this would give three strata of subjects (STD, STP and STN) of roughly the same size, a situation that was not foreseen when the study started, and the STN stratum was considered to be a subject group of particular interest. Therefore, this report in general presents tables and graphs for four strata: STD, STF, STP and STN. The reader needs to keep in mind that STF = STP + STN.

The adverse events have been analysed by means of descriptive statistics and qualitative analysis. Statistical significant testing has not been performed except when comparing the incidence of 11 pre-defined glucocorticosteroid side effects between treatment groups where Chi-square test without Yates' correction has been used.

In all analyses, whenever appropriate, the corresponding baseline (Visit 2) value has been used as a linear covariate.

All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

SUBJECTS

	Budesonide ≤ 9 mg	**Prednisolone ≤ 40 mg**	**Total**
No. planned			320
No. randomised	142	143	285
No. randomised and treated	138	134	272
Males/Females	68/70	64/70	132/140
Mean age (range)	37 (17-66)	37 (18-69)	37 (17-69)
No. analysed for efficacy	137	134	271
No. analysed for safety	138	134	272
No. completed	66	70	136

RESULTS

- EFFICACY RESULTS

Primary variable:

Budesonide affects BMD of the lumbar spine significantly less than prednisolone in steroid-naïve subjects (STN), whereas there is no indication of a difference among subjects with current (STD) or previous (STP) steroid intake. There is also no difference among the STF subjects (the

combined group of STP and STN). In the STN stratum, the difference was clear already after 6 months (the first on-treatment assessment).

Secondary variables:
The pattern of change in BMD in the other regions of the body was similar to that for lumbar spine but with smaller differences. Only one new fracture occured. The disease activity (CDAI) fell rapidly in both treatment arms in the patients with active disease; from 1 month about 50% of the patients were in remisssion in both treatment groups. Quality of life (IBDQ and SF-36) improved in both treatments, mainly IBDQ. There were no clear differences in response to the ACTH tests.

- SAFETY RESULTS
The incidence of AEs was high in both treatment groups. The most frequent SOCs occurring in the AE reporting were gastrointestinal disorders, endocrine disorders and general disorders. AEs within gastrointestinal disorders and general disorders were slightly more common in the budesonide group whereas AEs within endocrine disorders were more common in the prednisolone group. The overall incidence of treatment emergent GCS side effects was significantly higher in the prednisolone subjects($p=0.001$) as was the incidence of moon face ($p<0.0001$), insomnia ($p=0.011$), acne ($p=0.026$) and bruising easily ($p=0.012$). The number of subjects with serious adverse events was similar in the two treatment groups and the vast majority of the serious adverse events were symptoms of CD requiring hospitalisation. Only few subjects discontinued the study due to untolerable adverse events.

Reference:

Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn’s disease, 17 January 2005

Schoon EJ, Bollani S, Mills PR, Israeli E, Felsenberg D, Ljunghall S, Persson T, Haptén-White L, Graffner H, Bianchi Porro G, Vatn M, Stockbr ü gger RW Clinical Gastroenterology and Hepatology - February 2005 (Vol. 3, Issue 2, Pages 113-121)

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