Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease

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Abstract

***Background*—The relapse rate after steroid induced remission in Crohn's disease is high.**

***Aims*—To test whether oral pH modified release budesonide (3 × 1 mg/day) reduces the relapse rate and to identify patient subgroups with an increased risk of relapse.**

***Methods*—In a multicentre, randomised, double blind study, 179 patients with steroid induced remission of Crohn's disease received either 3 × 1 mg budesonide (n=84) or placebo (n=95) for one year. The primary study aim was the maintenance of remission of Crohn's disease for one year.**

***Results*—Patient characteristics at study entry were similar for both groups. The relapse rate was 67% (56/84) in the budesonide group and 65% (62/95) in the placebo group. The relapse curves in both groups were similar. The mean time to relapse was 93.5 days in the budesonide group and 67.0 days in the placebo group. No prognostic factors allowing prediction of an increased risk for relapse or definition of patient subgroups who derived benefit from low dose budesonide were found. Drug related side effects were mild and no different between the budesonide and the placebo group.**

***Conclusion*—Oral pH modified release budesonide at a dose of 3 × 1 mg/day is not effective for maintaining steroid induced remission in Crohn's disease.**

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Keywords: budesonide; Crohn's disease; maintenance of remission

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Glucocorticoids are effective in inducing remission in patients with active Crohn's disease.[1–3] However, the relapse rate of Crohn's disease in patients with glucocorticoid induced remission is high.[1 2] The European cooperative Crohn's disease study[2] showed that systemic glucocorticoids reduced the relapse rate in these patients. However, prolonged glucocorticoid treatment is associated with a substantial number of side effects.

Several pilot studies suggested effectiveness of oral budesonide in acute Crohn's disease.[4–8] This was confirmed in controlled clinical trials.[9–12] Similar remission rates of 53%,[9] 51%,[10] and 56%[12] were found with 9 mg budesonide/day in various studies with a low rate of steroid associated side effects in 26–29%. This side effect rate was not significantly different from that of placebo treated patients.[10] Greenberg *et al* found no significant long term suppression of plasma cortisol with 3 mg budesonide/day whereas 9 mg budesonide led to a reduction by about 30–50%.[10]

We therefore tested the efficacy and safety of oral pH modified release budesonide in a dose of 3 × 1 mg/day as maintenance therapy in patients with steroid induced remission of Crohn's disease. The formulation of budesonide used in this study has been shown to be effective in active Crohn's disease and to induce remission in 60% of patients with disease distal to the hepatic flexure.[12] In addition, we analysed a large group of patients with steroid induced remission to see whether various epidemiological, clinical, or laboratory parameters allow identification of patient subgroups with an increased risk of relapse.

Methods

This was a multicentre, placebo controlled, double blind, randomised study. The study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz and by seven other local ethics committees.

PATIENT SELECTION

Eligible patients were 18–70 years of age, with a confirmed diagnosis of Crohn's disease. Patients with active Crohn's disease (defined by a Crohn's disease activity index (CDAI) of greater than 200) entered the screening phase. They were treated with glucocorticoids according to the European cooperative Crohn's disease study dosing regimen until they reached remission.[2] Before entering the maintenance study they were required to have been in remission with 10 mg or 5 mg prednisolone equivalent for eight weeks. During the study period they received 3 × 1 mg budesonide or placebo for 12 months. Relapse of Crohn's disease was defined by an increase of the CDAI to at least 150 for more than two subsequent weeks, or a CDAI of at least 150 at the end of the study or at the last documented visit. If the patient stopped the study before one year (for example, because of non-compliance or adverse events) the last documented CDAI was used for calculation. Secondary outcome measures were time to relapse, analysis of subgroups with respect to relapse, and side effects.

Table 1 Patient characteristics

	Budesonide (n=84)	*Placebo (n=95)*
Sex (F/M)	48/36	58/37
Age (y)*	32 (11)	32 (10)
Duration of disease (months)*	67 (67)	60 (71)
Patients with previous therapy for Crohn's disease	76 (90.5%)	76 (80.0%)
Localisation of Crohn's disease†		
Stomach	3 (3.6%)	6 (6.4%)
Duodenum	5 (6.0%)	4 (4.3%)
Jejunum	2 (2.4%)	3 (3.2%)
Ileum	23 (27.4%)	25 (26.6%)
Terminal ileum	60 (71.4%)	65 (69.2%)
Caecum	54 (64.3%)	58 (61.7%)
Ascending colon	54 (64.3%)	51 (54.2%)
Transverse colon	51 (60.7%)	56 (59.6%)
Descending colon	54 (64.3%)	60 (63.8%)
Sigmoid colon	54 (64.3%)	60 (63.8%)
Rectum	44 (52.4%)	48 (51.1%)
CDAI at start of acute phase therapy*	311 (95)	299 (71)
CDAI at randomisation for maintenance of remission*	65 (43)	66 (38)

*Expressed as mean (SD), not significantly different between the two groups.
†Multiple nominations possible per patient.

STUDY MEDICATION

The budesonide formulation used in this study was a gelatine capsule containing approximately 400 Eudragit coated microgranules with a diameter of about 1 mm (Dr Falk Pharma, Freiburg, Germany). The pellets dissolve at a pH greater than 6.4. Placebo medication was identical to the budesonide capsules. Compliance was tested by counting the tablets returned at control visits.

INTERVENTION AND FOLLOW UP SCHEDULE

In the prestudy period at least three patient visits were documented: start of acute phase treatment; after six weeks; and after 10 weeks. At the start of the acute phase of treatment demographic data, distribution, and activity of Crohn's disease (CDAI) were documented. At randomisation and start of maintenance therapy the CDAI was calculated, and a complete physical examination and laboratory tests were performed. Patients were allowed to take only the study medication and no other treatment for Crohn's disease. Follow up visits were performed after 1, 2, 4, 6, 8, 10, and 12 months. At each follow up visit the CDAI was calculated. If the CDAI was 150 or higher, the patient was reinvestigated after two weeks. Relapse was defined as the CDAI remaining at 150 or above.

STATISTICS

The intention to treat population was defined as patients suffering from Crohn's disease who were in remission at the time of randomisation (CDAI less than 150) and received at least one dose of study medication. The initial sample calculation required 100 patients in each group to show a reduction of the recurrence rate by approximately one third under budesonide compared with placebo (recurrence rate 41.5% versus 60%) with a power of 80%. The study was terminated prematurely (84 patients in the budesonide group, 95 patients in the placebo group) since at that time the overall failure rate was high. An independent steering committee (P Bauer, Wien; R Gugler, Karlsruhe; H Lochs, Berlin; W-H Schmiegel, Bochum) broke the randomisation code and calculated from 500 simulations that if the study would be continued and all future patients would show the assumed difference of approximately 20% in the one year relapse rate between budesonide and placebo there would only be a 13.6% chance of finding a significant advantage of budesonide over placebo. Because of the resulting premature termination of the study only an explorative statistical evaluation was possible. Fisher's exact test (one sided, since it was postulated that budesonide is superior to placebo; α=5%) was used to compare relapse rates between the budesonide and the placebo groups. Fisher's exact test (two sided, α=5 %) was used to compare the incidence of side effects and the frequency of abnormalities in laboratory parameters between both treatment groups. Kaplan-Meier estimation and the log rank test were used to compare the time to relapse between both groups. The Wilcoxon-Mann-Whitney U test (α=5 %, two sided) was used to compare baseline data and CDAI during the course of the study. To compare the time course of the CDAI and of some laboratory parameters within groups the Wilcoxon-Pratt test (α=5 %, two sided) was used.

Results

Three hundred patients with acute Crohn's disease were screened, of which 108 (36%) dropped out during the acute phase treatment. Of 192 randomised patients, eight were not in remission (CDAI at least 150), and five did not take the study medication. Therefore, the "intention to treat" population of the randomised maintenance study consisted of 179 patients (84 budesonide, 95 placebo).

Baseline demographics were comparable between both treatment groups (table 1). Figure 1 shows that the relapse rate was similar in both treatment groups. About 50% of relapses occurred during the first three months. A relapse occurred in 67% of patients in the budesonide group and in 65% of patients in the placebo group. The median time to relapse was 93.5 days in the budesonide group and 67.0 days in the placebo group. The log rank test showed no significant differences

Table 2 Individual outcome of all patients

	Budesonide (n = 84)		*Placebo (n = 95)*	
	Remission	*Relapse*	*Remission*	*Relapse*
Relapse before one year	0	46 (54.8%)	0	44 (46.3%)
One year of study completed	20 (23.8%)	5 (6.0%)	19 (20%)	2 (2.1%)
Study stopped by steering committee	5 (6.0%)	0	6 (6.3%)	3 (3.2%)
Study stopped because of non-compliance	2 (2.4%)	4 (4.8%)	6 (6.3%)	11 (11.6%)
Study stopped because of adverse events	1 (1.2%)	1 (1.2%)	2 (2.1%)	2 (2.1%)
All patients	28 (33.3%)	56 (66.7%)	33 (34.7%)	62 (65.3%)

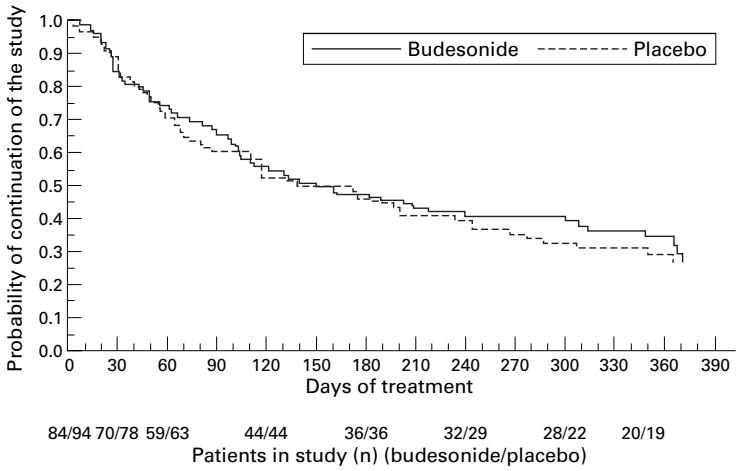

Figure 1 Time to relapse after randomisation and start of maintenance treatment.

between the two treatment groups. Twenty five patients in the budesonide group (29.8%; 20 (23.8%) in remission, five with relapse) and 21 patients in the placebo group (22.1%, 19 (20 %) in remission, two with relapse) completed the one year study period. Table 2 presents the outcome of all patients.

A subgroup analysis revealed that none of the following parameters influenced the relapse rate: age, sex, disease duration, previous surgery, previous steroid therapy, entrance CDAI, disease localisation, extraintestinal manifestations, perianal lesions during acute disease, response to acute phase treatment, blood sedimentation rate, and C reactive protein at time of randomisation.

The study medication was well tolerated. A total of 55.2% of patients in the budesonide group and 51.5% in the placebo group reported at least one adverse event, virtually all being manifestations of Crohn's disease. Adverse drug events according to the investigator were reported by 9.2% in the budesonide group and by 11.1% in the placebo group. Two patients in the budesonide group (2.3%) and four in the placebo group (4.0%) discontinued the study because of adverse events (table 2). Severe adverse events were only observed in the placebo group (one patient with pyelonephritis, one patient with abdominal pain of unknown aetiology).

Discussion

In our study the relapse rate of the maintenance therapy after steroid induced remission of Crohn's disease was 67% in the budesonide group and 65% in the placebo group. A high relapse rate after steroid withdrawal has also been observed in other studies. In the Getaid Study[13] a one year spontaneous relapse rate of 55% was found. In the study of Modigliani *et al*[14] it was 64% in the placebo arm. In the older ECCDS study[2] about 15% of patients who entered the study with active disease were in remission after one year. Steroid treatment increased the proportion of patients in remission after one year to about 45%.

Due to their side effects conventional steroids are not the treatment of choice for maintenance of remission in Crohn's disease. Several studies therefore have addressed the question whether other agents may be effective. A recent meta-analysis[15] comprising 10 studies including 1022 patients found that prophylactic treatment with mesalazine reduces the relative risk of Crohn's disease recurrence significantly (relative risk 0.63, 95% confidence interval 0.50 to 0.579). The French study of Gendre *et al*[16] showed that patients who are in remission for less then three months benefit from prophylactic mesalazine treatment. However, a more recent study[14] found that mesalazine may reduce the relapse rate in patients with steroid induced remission only in certain patient subgroups (high CDAI, white blood cell count greater than 9×10^9/l, and use of medical treatment in the month before inclusion).

Azathioprine, which is effective in inducing remission in patients with refractory or chronic active Crohn's disease,[17–19] has also been successfully used to maintain steroid induced remission.[20] Although azathioprine has been shown to be safe for maintenance therapy of Crohn's disease,[19 20] its use requires close follow up of patients and in some patients treatment has to be discontinued because of side effects. In addition, the long term use of immunosuppressives in young patients of reproductive age has to be carefully considered.

In view of the importance of the clinical problem non-systemic steroids have recently been tested as maintenance therapy for Crohn's disease. Our study failed to show an effect of 3×1 mg budesonide/day on the relapse rate. In addition, we could not identify patient subgroups where prophylactic budesonide treatment was beneficial. We cannot exclude the fact that administration of 3 mg budesonide in one daily dose would have been more effective. On the other hand, our data are in agreement with those of the studies by Löfberg *et al*[21] and Greenberg *et al*[22] using another budesonide formulation. These authors found that 3 mg or 6 mg of budesonide in one daily dose did not reduce the overall relapse rate of Crohn's disease, although 6 mg of budesonide/day significantly prolonged the median time to relapse (258 versus 92 days in the study by Löfberg *et al*[21] and 158 days versus 39 days in the study by Greenberg *et al*[22]). An explanation may be that 3 mg or 6 mg of budesonide/day shows no efficacy in Crohn's disease. Obviously, doses lower than those successfully used in acute Crohn's disease (9 mg/day) do not maintain remission of Crohn's disease over a one year period. However, experiments showing that budesonide exerts a long lasting dose dependent inhibition of proinflammatory cytokine secretion by mononuclear phagocytes[23] may offer new perspectives. Therefore, further maintenance studies assessing the efficacy and long term safety of higher doses of budesonide administered once daily in patients with Crohn's disease seem desirable.

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