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Maintenance treatment with budesonide 6 mg versus 9 mg once daily in patients with Crohn's disease in remission

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ABSTRACT

Background: In previous trials, budesonide 6 mg/day was able to prolong the time to relapse in patients with quiescent Crohn's disease and budesonide 9 mg/day was effective in active disease with limited side effects. The aim of this study was to compare the effectiveness of budesonide 9 mg *vs* 6 mg once daily on the maintenance of remission and occurrence of adverse events.

Methods: Double-blind, randomised trial in patients with Crohn's disease in remission. Patients were randomised to receive 6 mg/day or 9 mg/day of budesonide (Budenofalk®) without concomitant treatment for Crohn's disease. Endpoints were the time to relapse and relapse rates after one year.

Results: Seventy-six patients were randomised to 6 mg/day and 81 patients to 9 mg/day. Survival analysis showed no differences in the time to relapse. One-year relapse rates were not significantly different (6 mg group 24%; 9 mg group 19%). Any adverse event was reported in 61 and 68% of patients in the 6 mg and 9 mg groups, respectively; none of the 12 serious adverse events were drug related.

Conclusion: The one-year relapse rates were low and not significantly different between the group of patients treated with budesonide 6 mg *vs* 9 mg/day. Also, time to relapse and the number of adverse events were similar in both treatment groups.

KEYWORDS

Budesonide, Crohn's disease, IBD, RCT

INTRODUCTION

Crohn's disease is a chronic inflammatory disorder of the digestive tract. Medical treatment focuses primarily on the mucosal inflammation and corticosteroids are highly effective for the induction of remission of active Crohn's disease.[1,2] However, in various studies, the rate of relapses is high after withdrawal of corticosteroids. Long-term use of systemically active corticosteroids is associated with a substantial number of side effects, such as acne, moon face, hirsutism, buffalo hump, impaired glucose tolerance, mood disturbances and osteoporosis.[3] Furthermore, low doses of systemically active corticosteroids were ineffective for the prevention of relapses in previous studies.[4] The topically active synthetic steroid budesonide may overcome these disadvantages of long-term treatment with corticosteroids in Crohn's disease. Budesonide combines high intrinsic corticosteroid receptor affinity with a strong first pass effect in the liver of about 90% after oral administration.[5,6] Two oral formulations have been developed to release budesonide in the ileum and proximal colon,[7] or in the ileum and majority of the colon.[8-10]

In mild and moderately active Crohn's disease within the ileum or ascending colon, budesonide capsules in a dose of 9 mg/day have proven efficacy.[11-14] In a Cochrane systematic review, the efficacy was almost comparable with prednisone regimens with significantly less corticosteroid-associated adverse events.[15] Furthermore, treatment with budesonide capsules is able to prolong the time to relapse in patients with Crohn's disease in clinical remission. In two out of three dose-finding studies, 6 mg/day was

superior to 3 mg/day and to placebo with respect to the time to relapse.[16-18] However, relapse rates in these groups treated with budesonide 3 or 6 mg/day were not significantly lower compared with placebo at the end of a one-year treatment period. These findings were confirmed by a pooled analysis of these three studies and a similarly designed trial with two parallel groups (placebo and 6 mg/day).[19,20] In the pooled analysis, the median time to relapse was significantly prolonged from 154 days in the placebo group to 268 days in the budesonide 6 mg/day group. The relapse rate after one year was 59% in the placebo group, which was not significantly different from 51% in the patients treated with budesonide 6 mg daily. Since a dose relationship seems to exist in these maintenance trials, administration of budesonide in a higher dose of 9 mg/day may be more effective. The primary objective of the study was to evaluate if the time to relapse is prolonged under budesonide 9 mg/day compared with 6 mg/day, in patients with Crohn's disease in remission at study entry. Secondary objectives were to evaluate the percentage of patients in remission and to examine the safety of budesonide 6 mg and 9 mg/day over a treatment period of one year.

MATERIALS AND METHODS

Patient selection

Patients aged between 18 and 75 years with confirmed Crohn's disease were eligible for the study if they fulfilled the following criteria: Crohn's disease in remission for at least three months, but not more than 18 months, remission was defined as a Crohn's Disease Activity Index (CDAI) below 150 points;[21] disease locations previously confined to the ileum or colon except rectal and perianal disease. Patients who fulfilled one of the following criteria were not eligible for the study: bowel surgery within six months before randomisation; history of small bowel resections exceeding 80 cm; disease locations proximal to the ileum; severe hepatic disease defined by elevated liver enzymes of three times the upper normal limit, or renal disease with serum creatinine levels more than twice the upper normal limit; presence of diseases that may deteriorate due to corticosteroids (such as diabetes mellitus, glaucoma, aseptic bone necrosis, acute psychosis and severe hypertension); need for parenteral nutrition; presence of active systemic infections or gastroenteritis; and pregnancy or inadequate use of contraceptives during the trial.

This study was conducted in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996). Before recruitment of patients, the protocol was reviewed and approved by the local ethics committees. All patients gave their written informed consent before participation in the study.

Study drug and concomitant medication

Capsules containing pH-modified release pellets of budesonide (Budenofalk® 3 mg capsule) and placebo capsules with an identical appearance were manufactured by Losan Pharma GmbH, Neuenburg, Germany and supplied by Dr. Falk Pharma GmbH, Freiburg/, Germany. Patients were assigned to one of the two treatment groups by a randomisation list generated by the Rancode+ programme (version 3.6) of IDV, Gauting (Germany). Randomisation tables were stored in closed, nontransparent envelopes to be opened after closure of the database. For emergency reasons, closed envelopes containing the type of treatment were available on the site. These emergency envelopes were collected at the end of the trial and monitored for closure.

In group A, patients received three capsules of budesonide 3 mg once daily and in group B, patients received two capsules of budesonide 3 mg and one placebo capsule once daily.

At time of randomisation, prednisolone or methylprednisolone were accepted in a maximum dose of 20 and 16 mg/day, respectively, with a fixed tapering schedule within six weeks. Use of budesonide was permitted at the time of randomisation in a maximum dose of 9 mg/day, which had to be discontinued that day. Additional treatment with investigational agents, azathioprine, cholestyramine, cyclosporine or metronidazole, had to be stopped at least two weeks prior to randomisation. Furthermore, 5-aminosalicylates or other treatments for Crohn's disease, proton pump inhibitors and diuretics were not permitted during the trial after randomisation.

Trial design

The study was designed as a randomised, double-blind parallel group, multicentre clinical trial. One tertiary referral centre for inflammatory bowel disease and 32 regional centres (3 in Germany and 29 in the Netherlands) participated in the study. Eligible patients were randomly allocated to treatment with either budesonide 6 mg or 9 mg once daily for up to 52 weeks. Fixed outpatient visits were scheduled after 8, 24 and 52 weeks and additional visits were required in case of an increase in symptoms or adverse events (AEs). At each study visit, the CDAI was determined, and physical examination and laboratory tests were performed. All AEs, including signs and symptoms suggestive of corticosteroid-associated side effects, were recorded. Relapse was defined by a CDAI of more that 150 together with an increase of at least 60 points. If an increase in CDAI was likely explained by non-Crohn's disease causes, it was permitted to repeat the CDAI once and if it had normalised it was not considered to be a relapse. Time to relapse was defined as the time between the baseline visit and the first visit with a CDAI corresponding to a relapse.

Statistical analysis

Based on previous studies, we assumed an exponential disease-free survival and a relapse rate of 50% in the control group on budesonide 6 mg. We estimated that 95 patients per group were needed to detect an increase of at least 50% in time to relapse on budesonide 9 mg/day compared with 6 mg/day ($\alpha = 0.05$; $\beta = 0.20$). Patients who received at least one dose of study medication with at least one follow-up visit were included in the safety analysis and intention-to-treat (ITT) analysis. Kaplan-Meier estimates and log-rank tests of the survival distribution function were used for the analysis of the primary outcome measure time to relapse. The following covariates were included in the Kaplan-Meier analysis as strata: concomitant use of systemic corticosteroids at time of randomisation, disease location, smoking history, duration of disease, history of bowel resections, previous use of budesonide, and centre of inclusion. In the statistical analysis plan, 10, 15, 20 and 25% quantiles were used to obtain a 9 mg/6 mg ratio concerning time to relapse. Additionally, the median time to relapse (= 50% quantile) was estimated parametrically with SAS PROC LIFEREG assuming a Weibull distribution. The one-year relapse rates were analysed by Fisher's exact test. Baseline characteristics, secondary efficacy parameters and safety parameters were analysed by descriptive statistics. In case of missing values at the final examination, the last documented follow-up value was used. Results are given as mean ± standard deviation or median (range). The statistical evaluation was performed using SAS version 8.2.

Table 1. *Baseline characteristics according to study group*

	Budesonide 6 mg (n=76)	Budesonide 9 mg (n=81)
Sex (female/male)	47/29 (62/38)	45/36 (56/44)
Age (years)	35 (19-73)	35 (18-72)
Weight (kg)	69.5 (45-104)	74.9 (50-131)
Height (cm)	172 (150-198)	175 (154-194)
History of bowel resection	24 (32)	36 (44)
Smoking habits (never/ever)	30/46 (40/60)	35/46 (43/57)
Disease duration (years)	4.5 (0-32)	2.5 (0-49)
Disease involvement:		
• Ileum	72 (95)	77 (95)
• Caecum	42 (55)	41 (51)
• Ascending colon	24 (32)	24 (30)
• Transverse colon	15 (20)	18 (22)
• Descending colon	10 (13)	12 (15)
• Sigmoid colon	11 (15)	13 (16)
CDAI at study entry*	69 (-16-154)	76 (-41-165)
Medication (last 12 months):		
• Corticosteroids	33 (43)	28 (35)
• 5-Aminosalisylate	67 (88)	70 (86)
• Immunosuppressive	2 (3)	4 (5)

Values are given as median (range) or number (%). *In each treatment group the Crohn's Disease Activity Index (CDAI) was above 150 in one patient (protocol violation).

RESULTS

Patients

The recruitment was terminated after 160 patients had been included (22 in the tertiary referral centre), because of slow enrolment and because the observed overall relapse rate was far below the estimated rate. The enrolment period started in November 1997 and was discontinued in February 2001. Three patients were excluded from the ITT analysis and safety evaluation. One patient was lost to follow-up without any follow-up values, one patient did not take the study medication and one patient was randomised twice. Of the remaining 157 patients, 76 were assigned to the 6 mg/day group and 81 were assigned to the 9 mg/day group. The baseline characteristics did not differ significantly between the two treatment groups (*table 1*).

Early withdrawal from treatment

Out of 157 patients, 56 discontinued the trial prior to one year after baseline. The number of early terminations was equally distributed between the two treatment groups, 28 (37%) in the 6 mg/day group and 28 (35%) in the 9 mg/day group. A flow chart of study participation is shown in *figure 1*. In the 6 mg/day group, 17 out of 76 patients (22%) discontinued due to inadequate efficacy, 11 (14%) for other reasons and 48 (63%) completed the one-year follow-up in clinical remission. In the 9 mg/day group, 18 out of 81 patients (22%) discontinued due to inadequate efficacy, 10 (12%) for other reasons and 53 (65%) completed the one-year follow-up in clinical remission.

Efficacy: relapse-free survival

The relapse-free survival as a function of time is shown in *figure 2* for both treatment groups in the ITT analysis. By log-rank test, no statistically significant difference between the two groups was demonstrated (p=0.46). From the covariates included in the Kaplan-Meier analysis, concomitant use of corticosteroids at the time of randomisation was associated with the shortest time to relapse (p=0.03). No influence on time to relapse was shown by the covariates disease location, smoking history, duration of disease, history of bowel resections, previous use of budesonide and centre of inclusion. After one year, the probability of being relapse free was around 75% in both groups and the median time to relapse was far outside the observation interval and could not be estimated using nonparametric methods. The nonparametric Kaplan-Meier estimates of the 10% quantile were 124 days in the 6 mg

Figure 1. *Flowchart of patients during study participation*

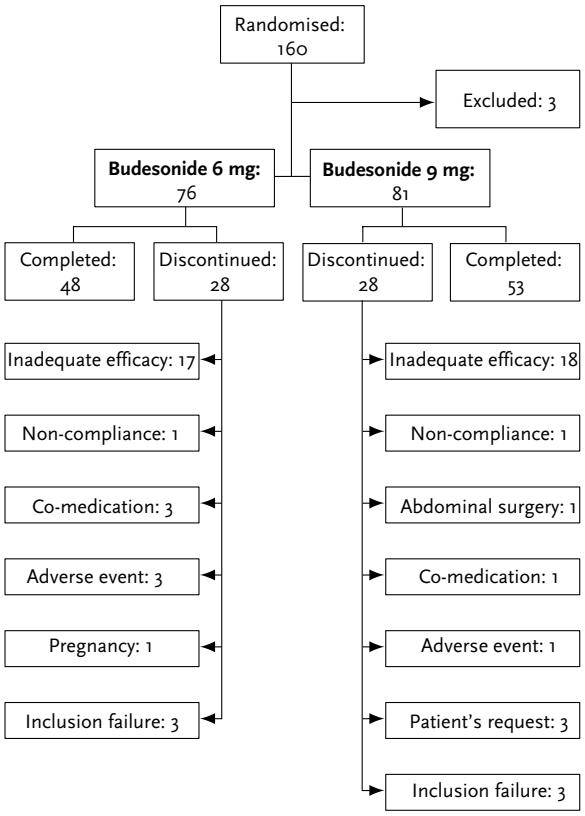
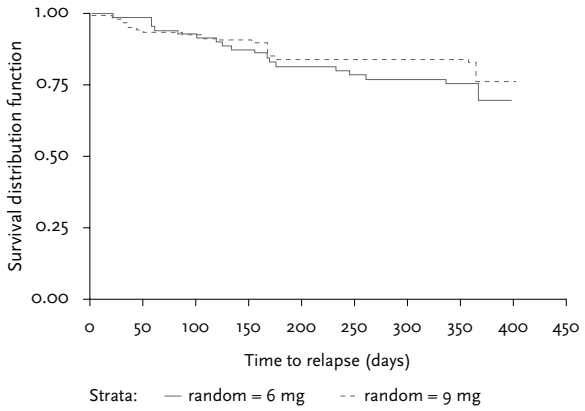


Figure 2. *Kaplan-Meier estimates of time to relapse with budesonide 6 mg/day and 9 mg/day in 157 patients with Crohn's disease in remission (ITT analysis)*



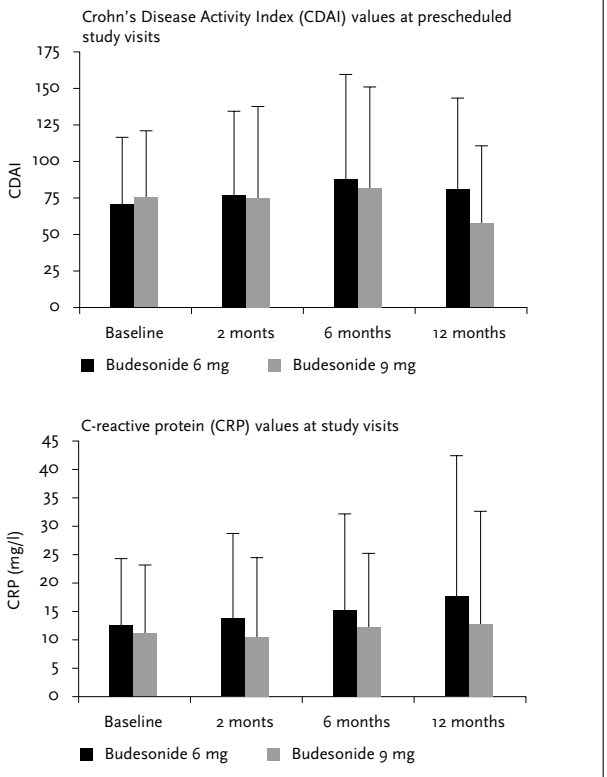
By log-rank test, no significant difference between the two treatment groups was observed (p=0.46). The hazards ratio with its 90% confidence interval is 0.773 (0.435-1.375).

group and 153 days in the 9 mg group, for the 15% quantile 165 days *vs* 175 days, and for the 20% quantile 232 *vs* 364 days, but the upper limit of the confidence interval was not estimable for the 20% quantile. The parametric estimates for the median time to relapse were 809 days (95% CI 360 to 1259) for the 6 mg group and 1049 days (95% CI 384 to 1713) for the 9 mg group. However, the maximal observation intervals in the study were 398 (6 mg group) and 402 days (9 mg group).

Efficacy: relapse rates

After the treatment period of one year, the relapse rate was not significantly different between the budesonide 6 and 9 mg groups (p=0.43). Relapse rates in the ITT were 24% (18/76) *vs* 19% (15/81) respectively and among those patients who completed the trial or discontinued due to a relapse 28% (18/65) *vs* 21% (15/71). The frequency of relapses was higher in the IBD referral centre compared with the non-IBD referral centres: 8 out of 22 patients (36%) and 25 out of 135 patients (19%), respectively. During the study period, the mean CDAI increased in the 6 mg/day group (from 71 ± 45 to 104 ± 86; not significant) and in the 9 mg/day group (from 76 ± 45 to 91 ± 84; not significant). Furthermore, C-reactive protein increased slightly in both groups from 12 ± 12 mg/l to 18 ± 23 mg/l in the 6 mg group and from 11 ± 12 mg/l to 15 ± 20 mg/l in the 9 mg group (*figure 3*). The erythrocyte sedimentation rate increased slightly in the 6 mg group from 16 ± 13 mm/h to 22 ± 1 mm/h, whereas it remained stable in the 9 mg group (15 ± 12 mm/h).

Figure 3. *The course of secondary efficacy parameters during maintenance treatment with budesonide*



Values represent mean ± SD.

Adverse events

In total, 195 AEs occurred in 101 patients during the study period. In the 6 mg group, 92 AEs occurred in 46 (61%) patients and in the 9 mg group, 103 AEs in 55 (68%) patients. An overview of all AEs classified by organ system is given in *table 2*. The intensity of the AEs was classified as mild or moderate in 94% of the cases. During the study period, no deaths occurred. A total of 12 serious adverse events (SAEs) were recorded in ten patients (*table 3*). The reason to classify these 12 events as serious was hospitalisation. None of these SAEs were clearly related to the study medication. Adverse events potentially related to corticosteroids are summarised in *table 4*. External steroid-related side effects such as acne, moon face and obesity were already present at baseline in 29% of the patients randomised to 6 mg/day and 22% of the patients in the 9 mg/day group. These initially present side effects resolved completely in nine patients (12%) in the 6 mg group and in six (7%) patients in the 9 mg group.

Table 2. *Summary of adverse events (numbers and %)*

Organ system	6 mg (n=76)	9 mg (n=81)
Endocrine	10 (13)	10 (12)
Eye	2 (3)	1 (1)
Gastrointestinal tract	9 (12)	11 (14)
Hepatobiliary tract	0	1 (1)
Infections	6 (8)	13 (16)
Injury, poisoning and procedure related	0	3 (4)
Metabolism and nutrition	4 (5)	9 (11)
Musculoskeletal and connective tissue	2 (3)	4 (5)
Nervous system	8 (11)	4 (5)
Pregnancy	2 (3)	0
Psychiatric	1 (1)	4 (5)
Renal and urinary tract	1 (1)	1 (1)
Reproduction and breast disorders	1 (1)	0
Skin and subcutaneous tissue	17 (22)	20 (25)
Surgery and medical procedures	1 (1)	0
Vascular	3 (4)	3 (4)
General disorders	5 (7)	5 (6)

DISCUSSION

The present trial was conducted to evaluate the time to relapse and one-year relapse rates, comparing 6 mg/day and 9 mg/day of budesonide in patients with quiescent Crohn's disease. Only 24% of patients treated with budesonide 6 mg/day relapsed within one year, compared with 19% of patients treated with 9 mg/day, without significant differences in time to relapse between both study groups. These relapse rates were lower than expected because in previous maintenance trials one-year relapse rates were over 50% in patients treated with budesonide 3 mg or 6 mg daily and placebo-treated controls.[16-18,20]

Although it was planned to include 190 patients in the present study, the recruitment was stopped after 160 patients for two reasons. First, due to the slow inclusion rate the study drug had reached its expiry date. And second, because of an overall (blinded) relapse rate far below the expected rates in the sample size calculation, it was highly unlikely that adding 30 more patients in this trial would result in different outcomes. Given 5% difference in relapse rates between both treatment groups in the ITT analysis, a much larger sample size would have been needed to reach

Table 4. *Summary of steroid-related adverse events*

	6 mg (n=76)	9 mg (n=81)
Acne	9 (12)	8 (10)
Moon face	6 (8)	9 (11)
Hirsutism	6 (8)	0
Headache	6 (8)	3 (4)
Abdominal pain	4 (5)	5 (6)
Obesity	4 (5)	7 (9)
Striae	2 (3)	4 (5)

Number of patients (%).

Table 3. *Serious adverse events during budesonide treatment*

Patient	Dose (mg)	Serious adverse event	Sex	Age (years)	Time (days)	Causal relation
1	6	Bartholini cyst surgery	F	21	34	Unlikely
2	6	Hypertensive crisis	M	67	354	Unrelated
3	6	Anal fistula	M	25	302	Unrelated
4	6	Extrauterine gravidity	F	34	290	Unrelated
5	9	Inguinal hernia	M	43	101	Unrelated
6	9	Vomiting, abdominal pain	M	22	164	Unlikely
7	9	Stab wound	M	23	62	Unrelated
8	9	Abdominal pain, diarrhoea	F	69	286	Unlikely
9	9	Psoas abscess	M	42	353	Unrelated
10	9	Ileus	M	34	141	Unlikely

F = female; M = male. Time is given in days from the start of the study medication to the first appearance of the serious adverse event.

significance, while the small difference of 5% between both groups may not be clinically relevant.

The magnitude of the difference in relapse rates in the present trial compared with previous placebo-controlled studies may have various explanations. First, the majority of patients (259 out of 270) in the studies by Greenberg, Löfberg, and Ferguson and colleagues were initially treated for active Crohn's disease with corticosteroids and randomised for the maintenance trials eight to 16 weeks after the onset of corticosteroid therapy if clinical remission was achieved.[16-18] In contrast, in the present study, clinical remission was induced by a variety of therapy modalities and the use of corticosteroids at the time of randomisation was associated with the shortest time to relapse. Therefore, this may partly explain the unexpected low relapse rate in the budesonide 6 mg group. The lower rate of relapses may also be explained by a potentially longer interval (3 to 18 months) between the onset of therapy for active Crohn's disease (i.e., treatment of last relapse) and inclusion in the present trial, compared with the previous maintenance trials. Due to the inclusion of patients with a longer disease-free period, selection of patients with a more benign course may have occurred, because the natural course of Crohn's disease may differ considerably between patients.[22] This potential selection bias was limited by excluding patients with an active disease-free period of more than 18 months. Finally, in the present study, the majority of patients were included by regional nonreferral IBD clinics. In these clinics, 25 out of 135 patients (19%) relapsed during the study period compared with eight out of 22 patients (36%) in the IBD referral centre. It may be so that patients treated in referral centres receive more aggressive disease and are more refractory to therapy.

Slow enrolment in the study was largely explained by the availability of azathioprine and methotrexate, which have proven efficacy in maintaining remission. If the patient was in remission on these immunosuppressants, it was considered unethical to discontinue them just for the study. Therefore, less than 5% of patients were on immunosuppressants in the year before randomisation, which were discontinued for intolerance in most of these cases.

After closure of recruitment in the present study, comparable low relapse rates were reported by Green and colleagues with budesonide 6 mg/day (19%) with a flexible dose between 3 and 9 mg/day (15%) in patients with Crohn's disease in remission.[23] A different definition of treatment failure was used, defined as moderate to severe symptoms over an eight-week period despite treatment with 6 mg in the fixed group and 9 mg in the flexible group, or a CDAI >200 with moderate to severe symptoms. Including a placebo group in the present trial would have solved the issue of the unexpected low relapse rates. Although scientifically justified, difficulties with patient recruitment were expected if a placebo group was included in the trial, because several maintenance modalities such as mesalamine, budesonide and azathioprine were widely available during the trial period.

In the present study, the frequency of adverse events was not different between the 6 mg/day and 9 mg/day treatment groups. In addition Greenberg and colleagues reported no significant differences in overall frequencies of adverse events within one year between groups treated with budesonide 3 mg/day (70%) or 6 mg/day (78%) or placebo (89%).[16] Focusing on potential corticosteroid-related events, no significant differences between placebo and budesonide 3 mg/day or 6 mg/day groups were observed in previous studies.[16-18] However, cortisol stimulation tests demonstrated mild adrenal suppression in the budesonide groups, compared with placebo.[16,18] In the present study, over 90% of the adverse events were of mild or moderate intensity and had usually resolved by the end of the study. None of the 12 serious adverse events had a probable relationship with the study medication. All these events were classified as serious because they required admission to hospital. The most frequently reported adverse events during the study period were likely related to corticosteroid treatment, such as acne, moon face and hirsutism. However, already at baseline, 29% of the patients receiving 6 mg/day and 22% of the patients receiving 9 mg/day showed external steroid-related side effects due to prior use of prednisone. Only 11% of patients in the 6 mg/day group and 15% in the 9 mg/day group developed corticosteroid-related side effects after baseline. Overall, the spectrum of adverse events during treatment with budesonide 6 mg/day or 9 mg/day is mild, which is in agreement with previous reports.

However, safety issues concerning osteoporosis due to long-term treatment with budesonide remain unanswered by this study. This is of importance as corticosteroids are considered to be an established risk factor for osteoporosis. As Crohn's disease in itself is also a risk factor for osteoporosis, the definite effects of corticosteroids on bone mineral density (BMD) remain less clear than initially thought.[24] Cino and colleagues reported a small but significant decrease in BMD over a two-year period in patients treated with budesonide compared with low-dose prednisone or nonsteroid therapy in a nonrandomised trial, which resulted in different phenotypes of Crohn's disease in the three cohorts.[25] In contrast, in a prospective randomised trial, Schoon and colleagues demonstrated significantly less loss in BMD during treatment with budesonide compared with prednisolone over a two-year period in corticosteroid-naive patients.[26]

In conclusion, a low relapse rate was achieved in patients with quiescent Crohn's disease, treated with budesonide 6 mg/day. No significant additional benefit was demonstrated by increasing the dose to 9 mg/day. On the other hand, the number of adverse events was similar in both treatment groups. In placebo-controlled trials, budesonide 6 mg daily

was able to postpone relapses, but was unable to prevent relapses in one year. Due to the absence of significant differences in the present trial, the efficacy of budesonide in prevention of relapses remains unproven. In individual cases, when dose escalation is needed, budesonide may be increased to 9 mg/day without a significant increase in adverse events over a one-year period.

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