Budesonide in the management of patients with Crohn's disease

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ABR THOMSON, D SADOWSKI, R JENKINS, G WILD. Budesonide in the management of patients with Crohn's disease. Can J Gastroenterol 1997;11(2):255-260. Modern medical therapy is increasingly based on evidence. The evidence presented here is that budesonide (Entocort, Astra Pharma) 9 mg/day is superior to placebo and equivalent to systemically active glucocorticosteroids in achieving disease remission in patients with active Crohn's disease, and in prolonging the recurrence time of symptomatic disease. Budesonide causes less disturbance to adrenal function than prednisone or prednisolone and may cause fewer steroid-associated symptoms. Thus, budesonide is the safer, more effective steroid of choice to treat patients with Crohn's disease.

Key Words: Budesonide, Crohn's disease, Steroid, Treatment

Le budésonide en traitement de la maladie de Crohn

RÉSUMÉ : La thérapeutique médicale moderne se fonde de plus en plus sur des preuves. Les preuves présentées ici concernent le budésonide (Entocort, Astra Pharma) qui, administré à raison de 9 mg/jour, s'est révélé supérieur au placebo et équivalent aux glucocorticostéroïdes administrés par voie orale pour ce qui est d'induire la rémission chez des patients atteints de maladie de Crohn évolutive et de prolonger l'intervalle entre les récurrences de symptômes. Le budésonide perturbe moins la fonction surrénalienne que la prednisone ou la prednisolone et provoquerait un moins grand nombre de symptômes associés aux cortiocstéroïdes. Le budésonide est donc un choix de corticostéroïde plus sûr et plus efficace pour le traitement des malades atteints de la maladie de Crohn.

While oral glucocorticosteroids ('steroids') are effective in the treatment of patients with active Crohn's disease (1-6), significant side effects occur that limit patient acceptance and safety (Table 1). In approximately 30% of patients long term steroid use is necessary because it is difficult to taper or discontinue the drug due to chronically active disease. For these reasons, new steroid preparations have been developed that are locally active at the gut of the intestine and have a high affinity for the steroid receptor in the intestinal tissue. The mechanisms of action of steroids in Crohn's disease are unknown but may relate to their inhibiting effect on natural killer cell activity (7,8). Budesonide (Entocort, Astra Pharma) is a recently developed glucocorticoid derivative with an affinity for the steroid receptor that is 100-fold higher than that of hydrocortisone. Budesonide undergoes extensive first-pass hepatic metabolism (9,10), resulting in metabolites with less systemic glucocorticoid activity than the

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TABLE 1
Percentage of patients reporting new side effects following initiation of prednisone therapy

Adverse effect	Percentage effected
Moon face	47
Acne	30
Infection	27
Skin rash	27
Arthritis, arthralgias	23
Back pain	20
Epigastric pain	18
Ecchymosis	17
Polyuria	15
Hypertension	13

Data from reference 29

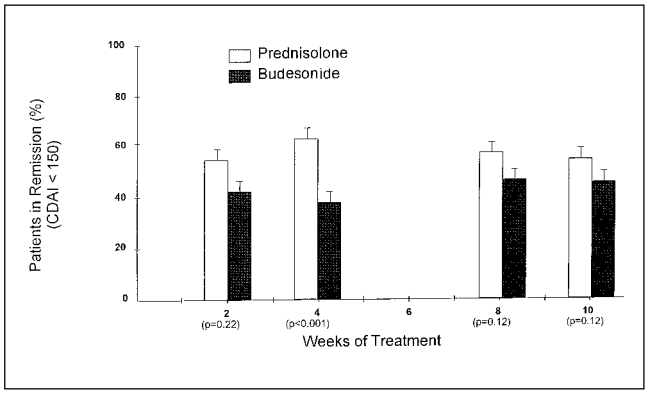

Figure 1) Mean (± standard error) proportion of patients with Crohn's disease in remission after treatment with prednisolone or budesonide. CDAI Crohn's disease activity index; n Number of patients. Reproduced with permission from reference 20

parent drug (11,12). Budesonide has been used effectively in the treatment of asthma and skin diseases without appreciable systemic activity (13). Enema formulations using budesonide have been used successfully for the topical treatment of ulcerative colitis (14-16). The recently developed controlled ileal release (CIR) formulation is intended to deposit budesonide predominantly in the ileum and ascending colon. Table 2 summarizes the evidence supporting the use of oral budesonide in the treatment of patients with active ileal Crohn's disease.

OPEN STUDIES

The first step towards establishing the efficacy and safety of a new therapeutic agent is to undertake open studies. Twenty-one patients with active ileocolonic Crohn's disease were treated with budesonide 3 mg tid for 12 weeks. Doses were reduced to 2 mg tid for six weeks and then 1 mg tid for a further six weeks (17). Over the 24-week course of study the modified Crohn's disease activity index (CDAI) score fell rapidly during the first four weeks of budesonide therapy. This was associated with a modest reduction in plasma cortisol concentrations. Other open studies support the potential for budesonide use (18).

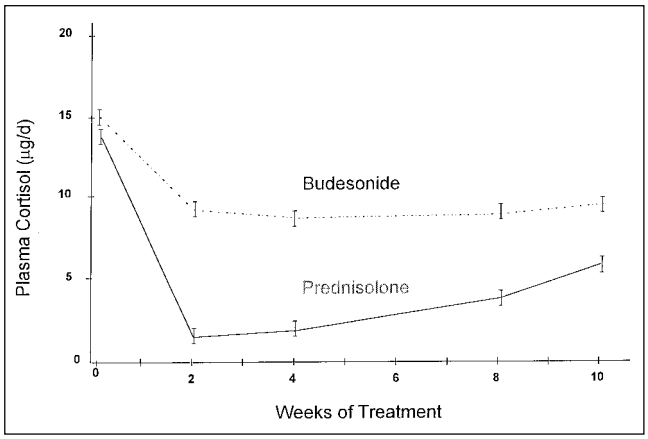

Figure 2) Mean (± standard error) plasma cortisol concentrations in patients with active Crohn's disease. Reproduced with permission from reference 20

Budesonide administered in an oral controlled release formulation gives an overall treatment result in patients with active ulcerative colitis approaching that of prednisolone, but without the suppression of plasma cortisol levels (19). This led the way for studies comparing the efficacies of budesonide, prednisone or prednisolone (the current standard glucocorticosteroid) and placebo.

BUDESONIDE VERSUS SYSTEMATICALLY ACTIVE STEROIDS

Rutgeerts and colleagues (20) undertook a double-blind randomized multicentre trial comparing the efficacy and safety of budesonide versus prednisolone. Their study included 176 patients with active Crohn's disease (CDAI greater than 200 at entry). Budesonide was given as 9 mg/day for eight weeks, then 6 mg/day for two weeks. This therapy was compared with prednisolone 40 mg/day for two weeks, 30 mg/day for two weeks, 25 mg/day for two weeks, and then 5 mg reductions until the end of the 10-week interval. Remission was defined as a CDAI of 150 or less and a 100 unit decline from the original level of the CDAI. At each time interval, the proportion of patients in clinical remission was numerically greater with prednisolone versus budesonide, although the difference was significant only at week 4 (Figure 1). In the first two weeks of therapy there was a rapid decline in the average CDAI in each group. Over the 10 weeks of the study, 53% of the patients taking budesonide entered remission (CDAI 150 or less), compared with 66% of patients on prednisolone (P=0.12). The mean score fell from 275 to 175 in the budesonide group, versus a fall from 279 to 136 in the prednisolone-treated patients (P=0.001). At most time points, patients in the prednisolone group had a greater decrease in the number of liquid or soft stools and a greater increase in body weight and sense of general well-being. It should be noted that in comparative studies of prednisolone and budesonide, because sample sizes of the groups

TABLE 2
Clinical efficacy of oral budesonide when used in patients with active ileal Crohn's disease

Author (reference)	Study medications (n)	Clinical remission*	Steroid side effects (%)†	Cortisol suppression (%)‡
Lofberg et al (19)	Budesonide CIR 3 mg tid for 12 weeks, 2 mg tid for six weeks, 1 mg tid for six weeks (21)	Reduction of mean CDAI from 268 to 122 at week 12 (P<0.001)	9.5	15
Rutgeerts et al (20)	Budesonide CIR 9 mg/day for eight weeks, then 6 mg/day for two weeks (88)	53% (at week 10)	33	37
	Prednisone 40 mg/day for two weeks, 30 mg/day for two weeks then tapering dose for six weeks (88)	66% (at week 10) (P=0.12)	55	89
Campieri et al (21)	Budesonide CIR 9 mg/day for eight weeks, 6 mg/day for two weeks, 3 mg/day for two weeks	60% (eight weeks)	–	58
	Budesonide CIR 4.5 mg bid for eight weeks, 6 mg/day for two weeks, 3 mg/day for two weeks	42% (eight weeks)	–	50
	Prednisolone 40 mg/day for two weeks, tapering dose over 10 weeks	60% (eight weeks)	–	84
Gross et al (30)	Budesonide 3 mg tid for eight weeks (34)	56% (eight weeks)	29	–
	Methylprednisolone 48 mg/day for one week, tapering dose over seven weeks (33)	73% (eight weeks) (P=0.237)	70	–
Greenberg et al (23)	Budesonide CIR 15 mg/day for eight weeks, 6 mg/day for two weeks (64)	43% (eight weeks)	38	67§
	Budesonide CIR 9 mg/day for eight weeks, 6 mg/day for two weeks (61)	51% (eight weeks)	26	69
	Budesonide CIR 3 mg/day for eight weeks, placebo for two weeks (67)	33% (eight weeks)	15	30
	Placebo for 10 weeks (66)	20% (eight weeks)	26	14
Lofberg et al (24)	Budesonide 6 mg/day for 12 months (32)	258 days	20 (at 12th month)	30
	Budesonide 3 mg/day for 12 months (31)	139 days	10	18
	Placebo (27)	92 days	0	5
Greenburg et al (23)	Budesonide 6 mg/day for 12 months (36)	178 days**	33	38¶
	Budesonide 3 mg/day for 12 months (33)	124 days	24	57
	Placebo (36)	39 days	11	80

*CIR Controlled ileal release; n number of patients. *Remission defined as a decrease in the Crohn's disease activity index (CDAI) to less than 150 and a 100 unit fall from baseline; †Percentage of patients reporting at least one steroid side effect not present at study initiation; ‡Proportion of patients with plasma cortisol levels below 150 nmol/L at any time during the study; §Proportion of patients with plasma cortisol levels below 200 nmol/L at any time during the study; ¶Proportion of patients with normal corticotrophin stimulation tests; **Maintenance study for Crohn's disease in remission. Study results are expressed as median time to clinical relapse*

are relatively small, there is the possibility of a type II error.

The decline in indicators of inflammation tended to be greater in the prednisolone versus the budesonide group. For example, at week 4 the decrease in mean erythrocyte sedimentation rate was greater in prednisolone patients versus budesonide patients (P=0.001), but the mean fasting blood glucose was higher in patients treated with prednisolone versus budesonide (P<0.001). Of importance, the decline in mean plasma cortisol concentration was greater at each time point in patients treated with prednisolone versus budesonide (Figure 2). The differences at weeks 4 and 8, but not at week 10, were statistically significant. The greater decline in mean plasma cortisol concentration in the prednisolone versus the budesonide group was associated with a higher incidence of adverse side effects: 29 of 88 patients treated with budesonide had corticosteroid-associated side effects while 48 of 88 patients treated with prednisolone had such side effects (P=0.003). In the prednisolone-treated group one patient had an intestinal perforation and one had an abdominal wall fistula.

Is there less benefit to giving budesonide once a day, as given by Rutgeerts and co-workers (20), rather than three times a day as used by Lofberg and colleagues (17). Campieri et al (21) studied 177 patients with Crohn's disease of the terminal ileum or ascending colon, in whom disease activity was reflected by a CDAI greater than 200. There were three treatment arms: budesonide 9 mg each morning or 4.5 mg bid, with the budesonide dose tapered to 6 mg after eight weeks and to 3 mg after 10 weeks, or prednisolone 40 mg each morning for two weeks, then 30 mg, with doses gradually reduced at the rate of 5 mg/week during the last three weeks of the 12-week study. Response was defined as a CDAI of 150 or less. After eight weeks of treatment there was no difference among the three groups, with 60% of the patients receiving morning budesonide in remission, compared with 42% of patients receiving budesonide bid and 60% of patients receiving morning prednisolone. The decline in morning cortisol at eight weeks was 195 nmol/L for the once-a-day budesonide and

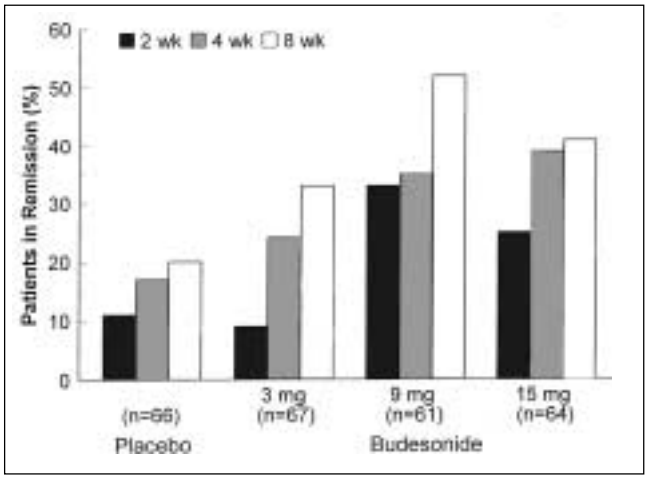

Figure 3) Percentage of patients with Crohn's disease in remission at each study visit. n Number of patients. Reproduced with permission from reference 22

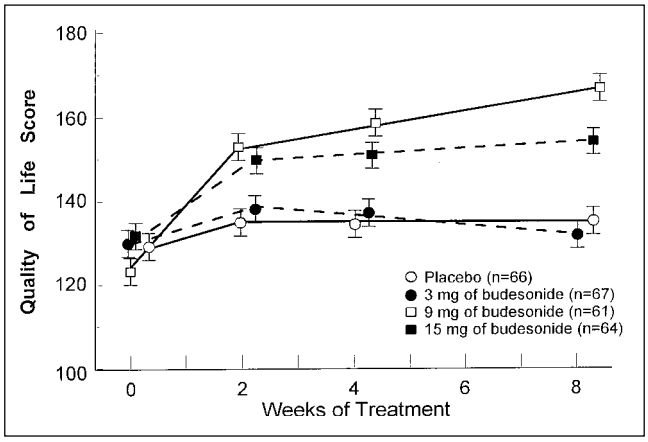

Figure 4) Mean (± standard error) scores on the quality of life questionnaire for each treatment group at each study visit. n Number of patients. Reproduced with permission from reference 22

132 nmol/L for the twice-a-day budesonide, compared with a decrease of 258 nmol/L for prednisolone (P=0.0035).

Impaired adrenal function, as assessed by a short adrenocorticotropic hormone (ACTH) stimulation test, was significantly more common in the prednisolone group (84%) than in the morning budesonide (58%) and in the budesonide bid (50%) groups (P=0.0023). Thus, a total dose of budesonide 9 mg given once or twice a day is comparable to prednisolone once a day in achieving clinical remission, without the same frequency of abnormal ACTH stimulation or reductions in plasma cortisol levels.

PLACEBO CONTROLLED STUDIES

Budesonide appears to be nearly comparable with prednisone or prednisolone in the treatment of active Crohn's disease, with fewer steroid-associated adverse effects. How does budesonide compare with placebo? Canadian investigators demonstrated the efficacy of budesonide versus placebo in the management of patients with active Crohn's disease (22). In a double-blind, multicentre trial, 258 patients were randomly assigned to receive placebo or one of three doses of budesonide: 1.5, 4.5 or 7.5 mg bid. Patients had active Crohn's disease of the ileum or ileum plus proximal colon. The primary outcome measure was clinical remission as defined by a CDAI score of 150 or less. The greatest decline in CDAI was in the first four weeks of treatment. After eight weeks of treatment, remission occurred in 51% of patients in the group receiving 9 mg of budesonide, 43% of those receiving 15 mg and 33% of those receiving 3 mg, compared with only 20% of those receiving placebo (P<0.01, P=0.009, P=0.13, respectively) (Figure 3). Location of disease, prior surgical resection, previous use of corticosteroids, sex or smoking status did not affect the outcome.

Improvements in quality of life, as measured by the patients' responses to the Inflammatory Bowel Disease Questionnaire, paralleled the remission rates (Figure 4). Those receiving 9 mg or 15 mg of budesonide per day had greater improvement in quality of life than did patients receiving placebo (P<0.001 and P=0.012, respectively). Patients receiving budesonide 9 mg/day had greater improvement in quality of life than those receiving 15 mg/day (P=0.034). Differences included improvements in the categories of social and emotional function.

There is an important practical point: patients receiving budesonide 15 mg/day in the Canadian study did not do as well as those receiving 9 mg/day. One possible interpretation is that if the patient does not respond to this dose, there would be no benefit to 15 mg budesonide.

Budesonide caused a dose-dependent reduction in basal- and corticotrophin-stimulated plasma cortisol concentrations, as well as in patient-reported corticosteroid-associated adverse effects. Basal plasma cortisol levels were similar in the three budesonide treatment groups throughout the year. Of interest, however, in the Canadian placebo controlled budesonide study (23): adverse reactions were reported by 25% of the patients receiving budesonide 9 mg/day, with an identical proportion of adverse reactions occurring in the patients given placebo.

MAINTENANCE OF REMISSION

Lofberg and colleagues (24) randomized 90 patients who had gone into remission after a previous 10-week course of therapy with either budesonide (using the pH-dependent formulation prepared by Astra) or prednisolone to 3 or 3 mg. (Entocort is now an approved and marketed product in 12 countries, and there is a substantial amount of literature in the public domain. If there are differences in the formulation and release patterns of the formulations, then clinical results obtained with one formulation may not necessarily apply to the other.) The patients were followed for up to 12 months. The median time to relapse or discontinuation of therapy was only 92 days in those on placebo,

compared with 139 days in those treated with budesonide 3 mg/day, and 258 days in those treated with budesonide 6 mg/day. An abnormal ACTH test was detected at three months in none of the patients on placebo, two of 22 on budesonide 3 mg/day and six of 23 treated with budesonide 6 mg/day.

Budesonide may also prolong the time to endoscopic recurrence after bowel resection surgery (25). In this study, patients with high disease activity appear to benefit from budesonide, but the overall patient groups did not show statistical benefit.

Similar results were obtained in Canada. In a double-blind multicentre trial, 105 patients with Crohn's disease were assigned to receive placebo or budesonide CIR in doses of 3 or 6 mg daily for one year (23). Patients receiving 6 mg of budesonide had a median time to discontinuation of therapy of 178 days, compared with 124 days in those receiving budesonide 3 mg, and 39 days in those receiving placebo. At one year the rate of relapse in the group receiving budesonide 6 mg was similar to the rates in the 3 mg and placebo groups. Basal plasma cortisol levels and the incidence of corticosteroid-associated effects were similar in the three groups. Thus, budesonide 6 mg/day prolongs the time that the Crohn's disease patient remains well after an acute attack.

The composite data for the use of budesonide for maintenance of remission in patients with Crohn's disease support the conclusion that this drug does not facilitate a sustained remission at one year. Thus, further trials are necessary before accepting the use of budesonide as maintenance therapy in all patients with Crohn's disease. Of note, there are almost no long term data available on the use of budesonide 9 mg/day in treating chronically active disease. The trials have been relatively short, and the remission data are associated with lower doses given to patients in remission.

Mesalamine does not facilitate steroid withdrawal (26), and it is unknown if this will be possible with budesonide. Some patients with chronically active Crohn's disease may have been on prednisone for protracted periods, and therapy with budesonide might be considered as an alternative. Although there currently are no specific guidelines regarding the best way to taper the dose of prednisone while introducing budesonide, a gradual tapering, as with any change in the dose of corticosteroids, is probably the best approach. The same care in the use of budesonide should be exercised as with any corticosteroid.

The evidence presented here is that budesonide 9 mg/day is superior to placebo and equivalent to systemically active glucocorticosteroids in achieving disease remission in patients with active Crohn's disease and in prolonging the time to recurrence of symptomatic disease. Budesonide causes less disturbance to adrenal function than prednisone or prednisolone and may cause fewer disturbances on steroid-associated symptoms. Thus, budesonide is the safer, more effective steroid of choice to treat patients with Crohn's disease. As suggested in two thoughtful editorials (27,28), the data allow us to be modestly optimistic about the future role of this new therapeutic modality.

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