Therapeutic benefits of budesonide in gastroenterology

Sarah O'Donnell and Colm A. O'Morain

Ther Adv Chronic Dis

[2010] 1(4) 177–186

DOI: 10.1177/
2040622310379293

© The Author(s), 2010.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Budesonide is a synthetic steroid of the glucocorticoid family with a high topical anti-inflammatory activity. Enteric-coated formulations resist gastric-acid degradation, delivering active drug to the small intestine and proximal colon. Budesonide has a high first-pass metabolism with minimal systemic absorption. It is therefore felt to cause fewer side effects than traditional glucocorticosteroids and to be generally well tolerated. The aim of this paper is to examine the utility of this medication in frequently encountered gastrointestinal conditions: Crohn's disease, ulcerative colitis, microscopic colitis and eosinophilic oesophagitis. A Medline search was performed to find published original research and review articles relating to the use budesonide in common gastroenterological conditions. The results showed that budesonide is efficacious in the induction and short-term maintenance of Crohn's disease. Budesonide is the best-documented treatment for microscopic colitis. It is well proven to be effective in the induction of remission in collagenous colitis but its use in lymphocytic colitis remains less well documented. In conclusion, budesonide is an effective glucocorticosteroid therapy for many chronic gastrointestinal diseases. In combination with its efficacy, the low incidence of serious side effects associated with this drug should keep it at the forefront in the therapeutic arsenal of any gastroenterologist.

Keywords: budesonide, Crohn's disease, eosinophilic oesophagitis, microscopic colitis, pouchitis, ulcerative colitis

Introduction

Budesonide is a synthetic steroid of the glucocorticoid family with a high topical anti-inflammatory activity. Budesonide was originally used as an inhaled treatment for inflammatory airway diseases. However, it has also been manufactured as oral controlled-release formulations. In this review we aim to examine the utility of this medication in frequently encountered gastrointestinal conditions: Crohn's disease, ulcerative colitis, microscopic colitis and eosinophilic oesophagitis. A Medline search was performed for available original research and review articles relating to the use budesonide in common gastroenterological conditions.

Enteric-coated formulations of budesonide resist gastric-acid degradation, delivering active drug to the small intestine and proximal colon [Fedorak and Bistritz, 2005]. Dissolution of the granules is delayed until the pH is greater than 5.5, normally occurring in the duodenum. A matrix of

ethylcellulose with budesonide then controls the release of the drug into the intestinal lumen in a time-controlled manner. On average 60–80% of the oral dose is absorbed in the ileum and colon [Edsbacker *et al.* 2003; Lundin *et al.* 2001]. Following oral administration and absorption, budesonide undergoes a 90% first-pass metabolism to form 6 β -hydroxybudesonide and 16 α -hydroxyprednisolone, both of which have less than 1% of the parent compound's corticosteroid activity [Edsbacker *et al.* 1987]. It has been hypothesized that chronic intestinal inflammation may increase the systemic exposure to budesonide. One study has found that the systemic availability was higher in Crohn's cases than in healthy volunteers (21% *versus* 12%, $p=0.009$) [Edsbacker *et al.* 2003]. However, another study found that the systemic availability in their cohort of Crohn's cases (9–12%) was the same as that found in healthy volunteers in the preceding study [Lundin *et al.* 2003]. This suggests that chronic inflammation does not increase

Correspondence to:
Sarah O'Donnell, MB, MRCP
Department of
Gastroenterology,
AMNCH, Tallaght, Dublin
24, Ireland
odonnnes2@tcd.ie

Colm A. O'Morain, DSc
(University of London),
DSc Honoris Causa
(University of Athens),
MSc, MD, MA, Dip. Imm.,
FACG, FEBG, FRCP,
FRCPI, FTCD, AGAF,
Consultant
Gastroenterologist,
Professor of Medicine,
Dean of Health Sciences
Department of
Gastroenterology,
AMNCH/Trinity College
Dublin, Dublin, Ireland

the systemic exposure to budesonide: perhaps its efficacy is mediated by an increased topical mucosal effect when inflammation is present although this remains unproven. Edsbacker and colleagues suggested that the increase in systemic availability in Crohn's patients over healthy volunteers seen in their study could be due to an inhibition of liver enzyme, CYP3A [Lundin *et al.* 2001], which can occur with inflammation [Morgan, 2001]. While subjects with active inflammatory bowel disease have been found to have similar small bowel transit times to healthy volunteers, active disease does impact on colonic transit. This rapid colonic transit may increase delivery of budesonide to the left colon in patients with active Crohn's disease [Lundin *et al.* 2001]. Food intake does not appear to effect uptake [Edsbacker *et al.* 2002; Lundin *et al.* 2001].

Side effects

Budesonide has a high first-pass metabolism with minimal systemic absorption. It is therefore felt to cause fewer side effects than traditional glucocorticosteroids and to be generally well tolerated (Table 1). A recent study pooled the safety data of five double-blind placebo-controlled trials. [Lichtenstein *et al.* 2009]. This pooled analysis found that the highest incidence rates of side effects were gastrointestinal and endocrine-related in both groups (budesonide 6 mg/day, $n=208$; placebo, $n=209$). The incidence rates were similar in each group, except for higher incidence of endocrine disorders in budesonide *versus* placebo patients ($p=0.0042$) caused by a higher overall occurrence of cutaneous glucocorticosteroid symptoms ($p=0.0036$) in the budesonide group. The percentage of patients

with normal adrenal function was significantly lower at 13 weeks, but not at 52 weeks (two studies) in the budesonide group. Similar rates of serious adverse events typically associated with traditional systemic glucocorticoids, including sepsis, cataracts, adrenal insufficiency were seen in both groups. This study concluded that budesonide is well tolerated in Crohn's disease for up to one year. Budesonide has been shown to better preserve bone mass compared with prednisolone in corticosteroid-naïve patients with active Crohn's disease [Schoon *et al.* 2005]. However, due to a lack of fractures during the follow-up period, a benefit of budesonide on fracture reduction could not be demonstrated. Measurements of osteocalcin, a marker of bone metabolism that correlates with osteoblast activity, demonstrated that budesonide did not impair the osteoblast activity of patients with active Crohn's disease at a dose of 9 mg/day [D'Haens *et al.* 1998].

Crohn's disease

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract characterized by periods of relapse and remission. The aim of treatment therefore is not only to induce remission but also to maintain remission in the longer term. This is a lifelong disorder that commonly presents during childhood and early adulthood and therefore treatments must be safe in the long term.

Induction of remission

The American Association of Gastroenterology, European Crohn's and Colitis Organisation and British Society of Gastroenterology have all recommended the use of budesonide for the

Table 1. Side effects associated with budesonide.

Frequency	System organ class	Undesirable effect
Common (>1/100 to <1/10)	Endocrine disorders	Cushingoid features
	Psychiatric disorders	Hypokalaemia
	Eye disorders	Behavioural changes
	Cardiac Disorders	Blurred vision
	Gastrointestinal disorders	Palpitations
	Skin disorders	Dyspepsia
		Skin reactions (urticaria, exanthema)
Uncommon (>1/1000 to <1/100)	Musculoskeletal	Muscle cramps
	Reproductive system	Menstrual disorders
Uncommon (>1/1000 to <1/100)	Nervous system	Tremor
Very rare (<1/10,000)	Musculoskeletal	Reduced growth velocity
		Anaphylactic reaction

induction of remission of mild-to-moderate ileo-colonic Crohn's disease [Dignass *et al.* 2010; Lichtenstein *et al.* 2006; Travis *et al.* 2006; Carter *et al.* 2004]. Two studies have shown that budesonide 9 mg/day for 8 weeks is more effective than placebo at inducing remission in active Crohn's disease, with remission rates of 48% and 51% in the budesonide arms (Table 2) [Tremaine *et al.* 2002; Greenberg *et al.* 1994], although this did not reach statistical significance in the second study due to high remission rate in the placebo group [Tremaine *et al.* 2002]. Both of these studies included mild-to-moderate Crohn's disease cases with ileal and/or proximal colonic involvement. The average Crohn's disease activity index (CDAI) was slightly higher in the first study and perhaps this explains the nonsignificant results of the study by Tremaine and colleagues: milder flares of Crohn's disease are more likely to remit spontaneously. In comparing budesonide with prednisolone for the induction of remission, budesonide has been found to be nearly as effective as prednisolone but with less pituitary–adrenal axis suppression and fewer side effects [Campieri *et al.* 1997; Rutgeerts *et al.* 1994]. Campieri and colleagues found no significant difference in efficacy between the two drugs: after 8 weeks of treatment, remission occurred in 60% of patients receiving budesonide 9 mg once daily or prednisolone 40 mg once daily

and in 42% of those receiving budesonide 4.5 mg twice daily ($p=0.062$) [Campieri *et al.* 1997]. However, Rutgeerts and colleagues found that while both were effective at inducing remission, prednisolone reduced CDAI scores further [Rutgeerts *et al.* 1994]. A recent meta-analysis concluded that budesonide is more effective than placebo or mesalamine for the induction of remission in Crohn's disease. Although short-term efficacy with budesonide is less than with conventional steroids, particularly in those with severe disease or more extensive colonic involvement, the likelihood of adverse events and adrenal suppression is lower [Seow *et al.* 2008]. After 8 weeks of treatment, budesonide was significantly more effective than placebo (relative risk [RR] 1.96, 95% confidence interval [CI] 1.19–3.23) or mesalamine (RR 1.63; 95% CI 1.23–2.16) for induction of remission.

Maintaining remission

The efficacy of budesonide in maintaining remission is less well proven. The pooled analysis of four randomized placebo-controlled trials found that budesonide 6 mg/day prolonged time-to-relapse compared with placebo, i.e. 268 days for budesonide *versus* 154 days for placebo-treated patients, $p=0.007$ [Sandborn *et al.* 2005]. Budesonide was effective in maintaining remission at 3 and 6 months; however, the relapse rates did not differ at 12 months. However, a

Table 2. Remission rates reported in budesonide studies.

Study	Site of CD	N	Comparison group	Remission rate
Thomsen <i>et al.</i> [1998]	Ileum, ascending colon or both	182	Bud 9 mg vs. mesalamine 2 g	62% vs. 36% at 16 weeks, $p < 0.001$
Tremaine <i>et al.</i> [2002]	Distal ileum or proximal colon	200	Bud 9 mg o.d. vs. 4.5 mg b.d. vs. pred	48% vs. 53% vs. 33%, NS
Greenberg <i>et al.</i> [1994]	Ileum or ileum and proximal colon	258	Bud 3 mg/9 mg/15 mg vs. pred	51%/43%/33% vs. 20% at 5 weeks, $p=0.001/p=0.009/p=0.13$.
Campieri <i>et al.</i> [1997]	Ileum and/or ascending colon	178	Bud 9 mg/4.5 mg b.d. vs. pred 40 mg	60%/42% vs. 60% at 12 weeks, $p=0.062$
Rutgeerts <i>et al.</i> [1994]	Ileum/ileocecal	176	Bud 9 mg for 8 weeks then 6 mg for 2 weeks vs. pred 40 mg for 2 weeks then taper	53% vs. 66% at 10 weeks, $p=0.12$
Bar-Meir <i>et al.</i> [1998]	TI and/or colon	201	Bud 9 mg vs. pred 40 mg for 2 weeks then taper	51% vs. 52.5% at 8 weeks, NS
Escher <i>et al.</i> [2004]	Ileum and/or ascending colon	48	Bud 9 mg for 8 weeks then 6 mg for 4 weeks vs. pred 1 mg/kg/day for 4 weeks then taper	55% vs. 71%, at 12 weeks, $p=0.25$
Levine <i>et al.</i> [2003]	—	33	Bud 9 mg vs. pred 40 mg	47% vs. 50% at 12 weeks, NS

CD, Crohn's disease; N, number of participants included; bud, budesonide; b.d., twice daily; NS, nonsignificant; o.d., once daily; pred, prednisolone.

more recent meta-analysis, including eight trials comparing budesonide with placebo for maintenance of remission, found that budesonide 6 mg/day was no more effective than placebo at 3 months (RR 1.25; $p=0.05$), 6 months (RR 1.15; $p=0.14$), or 12 months (RR 1.13; 95% CI 0.94–1.35; $p=0.19$) [Benchimol *et al.* 2009]. However, budesonide 6 mg did result in slight improvements in CDAI scores when assessed at 6 months (weighted mean differences [WMD] -24.3 ; $p=0.03$) and 12 months (WMD -23.49 ; $p=0.05$) and in the mean time-to-relapse of disease (WMD 59.93 days; $p=0.004$). Just one randomized control trial has examined the efficacy of budesonide compared with mesalazine in the maintenance of medically induced remission in Crohn's disease [Mantzaris *et al.* 2003]. The relapse rates in the budesonide group were significantly lower than in the mesalazine group (55% *versus* 82%; $p=0.045$). Patients assigned to budesonide also remained in remission longer (241 ± 114 days *versus* 147 ± 117 days; $p=0.003$). Not only was budesonide found to be more effective, but it was also associated with improved quality of life (QOL) of patients with steroid-dependent Crohn's disease compared with mesalazine. Treatment of steroid-induced medical remission for 1 year with azathioprine is however associated with lower relapse rates and improved maintenance of mucosal healing than with budesonide [Mantzaris *et al.* 2009].

Prevention of recurrence

Two studies have assessed budesonide in the prevention of postoperative recurrence of Crohn's disease. In the first of these, the efficacy of oral budesonide for prevention of endoscopic recurrence was evaluated in patients undergoing resection for ileal or ileocecal Crohn's disease, comparing budesonide 6 mg with placebo [Hellers *et al.* 1999]. Oral budesonide offered no benefit in the prevention of endoscopic recurrence after surgery for ileal/ileocecal fibrostenotic Crohn's disease but decreased the recurrence rate in patients who had undergone surgery for disease activity. There was a high withdrawal rate in this study. The second study compared budesonide 3 mg with placebo and while the effect of budesonide was superior to placebo in terms of the endoscopic and histopathological score, time-to-failure, CDAI, patients' global judgement and rate of side effects, the increase in efficacy was small and the power for detecting differences

versus placebo was too low to be statistically significant [Ewe *et al.* 1999].

Ulcerative colitis

There is limited data relating to the use of budesonide in ulcerative colitis. Two studies have found that budesonide is efficacious in ulcerative colitis but the number of cases in both studies were small. In steroid-dependent ulcerative colitis, budesonide 9 mg/day was effective in reducing the clinical activity score and rendering patients free of systemic steroid dependence [Keller *et al.* 1997]. Budesonide 10 mg/day resulted in similar endoscopic score reductions to prednisolone 40 mg/day in extensive or left-sided colitis [Löfberg *et al.* 1996]. Budesonide was given as 6 mg in the morning and 4 mg in the evening initially. The budesonide capsule contained acid-resistant pellets with a sustained-release profile to deliver active drug throughout the passage through the colon. However, when the endoscopic and microscopic appearances were examined according to location, the prednisolone group showed significantly better endoscopic and histologic scores in the distal colon. This is presumably due to the predominant drug delivery of budesonide in the proximal colon. Pouchitis is the major long-term complication after ileal-pouch anal anastomosis for ulcerative colitis. The cumulative risk of having one or more episodes of pouchitis varies from 15% to 53% in patients who have ulcerative colitis [Mahadevan and Sandborn, 2003]. Twenty consecutive patients with active pouchitis, not responding after 1 month of antibiotic treatment, were treated with budesonide controlled ileal release 9 mg/day for 8 weeks [Gionchetti *et al.* 2007]. Fifteen of 20 patients achieved remission. The median total Pouchitis Disease Activity Index (PDAI) scores before and after therapy were, respectively, 14 (range 9–16) and 3 (range 2–10) ($p < 0.001$). Remission was defined as a combination of PDAI score of ≤ 2 , endoscopic score of ≤ 1 and total PDAI score of ≤ 4 .

Budesonide foams and enemas have also been used in the treatment of distal colitis. Budesonide enemas have been found to be effective and well tolerated. The lowest effective dose appears to be 2 mg/100 ml [Lindgren *et al.* 2002; Hanauer *et al.* 1998]. Budesonide enema 2 mg/100 ml appears to be as efficient and well tolerated as 5-aminosalicylic acid (5-ASA) enema in the treatment of active distal ulcerative colitis and proctitis [Lémann *et al.* 1995].

The clinical remission rate at 4 weeks was, however, 38% for patients treated with budesonide enema but 60% for those treated with 5-ASA enema ($p=0.03$). Budesonide foam and enemas have been found to be equally as effective as other steroid foam and enema preparations but with less effect on the plasma cortisol level thus potentially minimizing steroid side effects [Hammond *et al.* 2004; Bar-Meir *et al.* 2003; The Danish Budesonide Study Group, 1991]. Foam spreads to a maximum of between 11 and 40 cm, thus reaching the sigmoid colon in all patients and even extending into the distal third and the middle of the descending colon in some patients [Brunner *et al.* 2005]. While budesonide enema and foam have similar efficacy to each other, in one study patients preferred foam [Gross *et al.* 2006].

Microscopic colitis

Budesonide is the best-documented treatment for microscopic colitis. Chronic diarrhoea has been reported in 4–5% of individuals in Western populations. Microscopic colitis, previously reported as rare, is increasingly being recognized as a common cause of chronic diarrhoea; particularly in elderly women. Its peak incidence is in 60–70-year-old individuals. In a Swedish epidemiologic study, the annual incidences of collagenous colitis and lymphocytic colitis were found to be equal to the incidence of Crohn's disease in Sweden, and combined rates approached the incidence of ulcerative colitis [Olesen *et al.* 2004]. Epidemiologic studies have suggested an increasing incidence over the last few decades [Pardi *et al.* 2007; Olesen *et al.* 2004], although it remains unknown whether this is a true rise in incidence or merely reflects an increased awareness and improved diagnosis through the routine taking of colonic biopsies in the investigation of chronic diarrhoea even in those with endoscopically normal colons. Microscopic colitis was diagnosed in 10% of all patients with nonbloody diarrhoea referred for colonoscopy and in almost 20% of those older than 70 years. Microscopic colitis comprises two distinct histological diagnoses: collagenous colitis and lymphocytic colitis. In collagenous colitis, a thickening of the subepithelial collagen layer is seen, along with a chronic mononuclear inflammation in the lamina propria. Lymphocytic colitis is characterized by an increased number of intraepithelial lymphocytes, but the collagen layer is normal.

Treatment of microscopic colitis was in the past based on observational studies and anecdotal evidence. Therapies have included traditional corticosteroids, budesonide, 5-ASA compounds, azathioprine, methotrexate, cyclosporine, antibiotics, bismuth subsalicylate, cholestyramine, octreotide, ketotifen, verapamil, pentoxifylline, loperamide and dietary modifications [Chande *et al.* 2008a, 2008b]. Few randomized control trials have been carried out. The fluctuating clinical course of microscopic colitis, characterized by spontaneous remission periods may lead to bias in uncontrolled studies. Chande and colleagues made the observation that patients tend to be included in studies when their symptoms are severe, and the improvement with treatment may be related to the natural history of their disease [Chande *et al.* 2009]. The benefit of budesonide in both the induction and maintenance of microscopic colitis has, however, been demonstrated in a number of randomized control trials, although to date numbers have been small.

Three randomized control trials have demonstrated an effect of budesonide in the induction of remission in collagenous colitis (Table 3). Baert and colleagues evaluated 28 patients' response to budesonide 9 mg/day ($n=14$) or placebo daily for 8 weeks [Baert *et al.* 2002]. Patients' response was evaluated both clinically and histologically. At 8 weeks, nonresponders received open-label budesonide for 8 weeks. Clinical response was defined as at least 50% decrease in disease activity score. Eight of 14 patients in the budesonide group *versus* 3 of 14 in the placebo group showed a clinical response after 8 weeks. Histologically, there was no change in the mean thickness of the collagen band but a significant decrease in the lamina propria infiltrate in the budesonide group. Similarly Miehke and colleagues randomized 51 patients with collagenous colitis to budesonide 9 mg/day ($n=26$) or placebo ($n=25$) for 6 weeks [Miehke *et al.* 2002]. The clinical remission rate was significantly higher in the budesonide group than the placebo group, 76.9% *versus* 12.0% respectively, based on intention to treat, $p < 0.001$. Histological improvement was observed in 60.9% of the budesonide group but only in 4.5% of the placebo group. Finally Bonderup and colleagues recruited 20 patients to budesonide 9 mg/day for 4 weeks, 6 mg/day for 2 weeks and 3 mg/week for 2 weeks or placebo [Bonderup *et al.* 2003]. All 10 patients receiving budesonide had a clinical response compared with only 2 in the placebo group. Once again,

Table 3. Induction of remission in microscopic colitis.

Study	Histological diagnosis	Number of patients	Comparison groups	Results
Baert <i>et al.</i> [2002]	Collagenous colitis	28	Bud 9 mg vs. pred	57% vs. 21% clinical response at 8 weeks
Miehlke <i>et al.</i> [2002]	Collagenous colitis	51	Bud 9 mg vs. pred	77% vs. 12% clinical remission at 6 weeks
Bonderup <i>et al.</i> [2003]	Collagenous colitis	20	Bud 9 mg for 4 weeks then 6 mg for 2 weeks then 3 mg for 2 weeks vs. pred	100% vs. 20% clinical response at 8 weeks
Miehlke <i>et al.</i> [2009]	Lymphocytic colitis	42	Bud 9 mg vs. pred	86% vs. 48% clinical remission at 6 weeks

Bud, budesonide; pred, prednisolone.

a significant reduction in both inflammation and thickness of the collagen layer was observed. All three studies concluded that treatment was safe and well tolerated. Eight of 10 patients in Bonderup and colleagues study had a relapse of symptoms within 8 weeks of treatment discontinuation, demonstrating the need for a maintenance therapy. The long-term outcome of 33 patients was assessed after induction of remission with budesonide 9 mg for 6 weeks in another study [Miehlke *et al.* 2005]. During a median follow up of 16 months, clinical relapse occurred in 20 patients (61%). This occurred within a median 2 weeks (range 1–104 weeks). A patient age of less than 60 was identified as a significant risk for relapse. These observations that the remission induced by budesonide is short lived underscored the need to study maintenance therapies for collagenous colitis.

Two studies have evaluated the safety and efficacy of long-term therapy with oral budesonide. [Bonderup *et al.* 2009; Miehlke *et al.* 2008]. In both studies, patients with active collagenous colitis were treated with open-label budesonide therapy, 9 mg/day, for 6 weeks. In total, 80 of 90 patients in whom remission was induced were then randomized to either placebo or budesonide 6 mg/day maintenance therapy and followed for 6 months. Both studies found a significantly lower relapse rate in the budesonide group. The pooled odds ratio for maintenance of clinical response was 8.82 (95% CI 3.19–24.37), with a number needed to treat of two patients [Chande *et al.* 2009]. In the first of these two studies, 12 of 42 patients experienced a mild adverse event during the open-label induction period, and one patient withdrew due to leg cramps [Miehlke *et al.* 2008]. In the maintenance period, 4 of 17

reported mild adverse reactions. In the second study, eight patients in each group reported adverse events but none were related to the study medication [Bonderup *et al.* 2009]. It has also been shown that 6 weeks treatment with oral budesonide significantly improves QOL in patients with collagenous colitis [Madisch *et al.* 2005].

The effect of budesonide in collagenous colitis may be multimodal. Bile salt malabsorption is frequent in collagenous colitis and may play a role in its pathophysiology. The ⁷⁵SeHCAT test is an indirect test for the active uptake of bile acids. One study has shown that treatment with budesonide 9 mg/day for 12 weeks results in the normalization of the ⁷⁵SeHCAT test and a reduction of bile salt synthesis in patients with initially high synthetic rates. [Bajor *et al.* 2006] These results suggest that the effect of budesonide in collagenous colitis may in part be due to decreased bile acid load on the colon. Another study has suggested that budesonide restores normal activation of eosinophils and T cells, which is accompanied by a clinical remission [Wagner *et al.* 2009].

The treatment of lymphocytic colitis is poorly defined. To date, only one randomized control trial has evaluated the effect of budesonide on the induction of remission [Miehlke *et al.* 2009]. Budesonide 9 mg/day successfully induced remission in patients with lymphocytic colitis after 6 weeks. A significant improvement in histology was also seen.

Eosinophilic oesophagitis

Eosinophilic oesophagitis is a clinicopathologic disorder characterized clinically by episodes of food impaction, dysphagia and proton-pump inhibitor-resistant reflux symptoms, and

histologically by greater than 15 eosinophils per high-powered field (EO/hpf) accompanied by other suggestive findings such as eosinophil degranulation, surface accentuation, basal cell hyperplasia and microabscesses.

Corticosteroid in the form of prednisolone and fluticasone has been shown to be an effective treatment for eosinophilic oesophagitis [Liacouras and Ruchelli, 2004; Arora *et al.* 2003; Teitelbaum *et al.* 2002]; however, both treatment strategies are flawed. While systemic steroids are effective for cases of severe oesophagitis complicated by dysphagia and strictures, they have the potential for systemic toxicity. Topical steroid therefore is a treatment of choice to minimize side effects. Oral fluticasone is effective but difficult to administer properly. In an attempt to make delivery of topical steroid to the oesophagus, oral viscous budesonide has been trialled in cases of eosinophilic oesophagitis. To date, only one retrospective study has evaluated response of symptoms, endoscopic and histologic findings, efficacy, and safety of treatment in children with eosinophilic oesophagitis receiving oral viscous budesonide [Aceves *et al.* 2007]. A significant reduction in the mean number of EO/hpf was demonstrated, 87 EO/hpf before treatment *versus* 7 EO/hpf after ($p < 0.0001$). The mean symptom score fell from 4.4 to 0.8, $p < 0.0001$.

Conclusion

In conclusion, budesonide is an effective glucocorticosteroid therapy for many chronic gastrointestinal diseases. In combination with its efficacy; the low incidence of serious side effects associated with this drug should keep it forefront in the therapeutic arsenal of any gastroenterologist.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Colm O'Morain is on the international advisory board of Abbott, Schering Plough, and Shire pharmaceutical companies. He has unrestricted educational grants from Abbott and Schering Plough.

References

- Aceves, S.S., Bastian, J.F., Newbury, R.O. and Dohil, R. (2007) Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am J Gastroenterol* 102: 2271–2279.
- Arora, A.S., Perrault, J. and Smyrk, T.C. (2003) Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc* 78: 830–835.
- Baert, F., Schmit, A., D'Haens, G., Dedeurwaerdere, F., Louis, E., Cabooter, M. *et al.* (2002) Belgian IBD Research Group; Codali Brussels. Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. *Gastroenterology* 122: 20–25.
- Bajor, A., Kilander, A., Gälman, C., Rudling, M. and Ung, K.A. (2006) Budesonide treatment is associated with increased bile acid absorption in collagenous colitis. *Aliment Pharmacol Ther* 24: 1643–1649.
- Bar-Meir, S., Chowers, Y., Lavy, A., Abramovitch, D., Sternberg, A., Leichtmann, G. *et al.* (1998) Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. *Gastroenterology* 115: 835–840.
- Bar-Meir, S., Fidler, H.H., Faszczuk, M., Bianchi Porro, G., Sturniolo, G.C., Mickisch, O. *et al.* International Budesonide Study Group (2003) Budesonide foam vs. hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis. *Dis Colon Rectum* 46: 929–936.
- Benchimol, E.I., Seow, C.H., Otley, A.R. and Steinhart, A.H. (2009) Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* CD002913.
- Bonderup, O.K., Hansen, J.B., Birket-Smith, L., Vestergaard, V., Teglbaerg, P.S. and Fallingborg, J. (2003) Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. *Gut* 52: 248–251.
- Bonderup, O.K., Hansen, J.B., Teglbaerg, P.S., Christensen, L.A. and Fallingborg, J.F. (2009) Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. *Gut* 58: 68–72.
- Brunner, M., Vogelsang, H., Greinwald, R., Kletter, K., Kvaternik, H., Schrolnberger, C. *et al.* (2005) Colonic spread and serum pharmacokinetics of budesonide foam in patients with mildly to moderately active ulcerative colitis. *Aliment Pharmacol Ther* 22: 463–470.
- Campieri, M., Ferguson, A., Doe, W., Persson, T. and Nilsson, L.G. (1997) Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 41: 209–214.
- Carter, M.J., Lobo, A.J. and Travis, S.P.L.; on behalf of the IBD Section of the British Society of Gastroenterology (2004) Guidelines for the

- management of inflammatory bowel disease in adults. *Gut* 53(Suppl V): V1–V16.
- Chande, N., MacDonald, J. and MacDonald, J. (2008a) Interventions for treating collagenous colitis. *Cochrane Database Syst Rev* 2: CD003575.
- Chande, N., MacDonald, J. and MacDonald, J. (2008b) Interventions for treating lymphocytic colitis. *Cochrane Database Syst Rev* 2: CD006096.
- Chande, N., MacDonald, J. and MacDonald, J. (2009) Interventions for treating microscopic colitis: a Cochrane inflammatory bowel disease and functional bowel disorders review group systematic review of randomized trials. *Am J Gastroenterol* 104: 235–241.
- D’Haens, G., Verstraete, A., Cheyngs, K., Aerden, I., Bouillon, R. and Rutgeerts, P. (1998) Bone turnover during short-term therapy with methylprednisolone or budesonide in Crohn’s disease. *Aliment Pharmacol Ther* 12: 419–424.
- Dignass, A., Van Assche, G., Lindsay, J.O., Lémann, M., Söderholm, J., Colombel, J.F. *et al.* (2010) The second European evidence-based consensus on the diagnosis and management of Crohn’s disease: current management. *J Crohn’s Colitis* 4: 28–62.
- Edsbacker, S., Andersson, P., Lindberg, C., Paulson, J., Rytfeldt, A. and Thalen, A. (1987) Liver metabolism of budesonide in rat, mouse, and man. Comparative aspects. *Drug Metab Dispos* 15: 403–411.
- Edsbacker, S., Bengtsson, B., Larsson, P., Lundin, P., Nilsson, A., Ulmius, J. *et al.* (2003) A pharmacoscintigraphic evaluation of oral budesonide given as controlled release (Entocort) capsules. *Aliment Pharm Ther* 17: 525–536.
- Edsbacker, S., Larsson, P. and Wollmer, P. (2002) Gut delivery of budesonide, a locally active corticosteroid, from plain and controlled-release capsules. *Eur J Gastroenterol Hepatol* 14: 1357–1362.
- Escher, J.C. for the European Collaborative Research Group on Budesonide in Paediatric IBD (2004) Budesonide versus prednisolone for the treatment of active Crohn’s disease in children: a randomized, double-blind, controlled, multicentre trial. *Eur J Gastroenterol Hepatol* 16: 47–54.
- Ewe, K., Böttger, T., Buhr, H.J., Ecker, K.W. and Otto, H.F. (1999) Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn’s disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group. *Eur J Gastroenterol Hepatol* 11: 277–282.
- Fedorak, R.N. and Bistriz, L. (2005) Targeted delivery, safety, and efficacy of oral enteric-coated formulations of budesonide. *Adv Drug Del Rev* 57: 303–316.
- Gionchetti, P., Rizzello, F., Poggioli, G., Pierangeli, F., Laureti, S., Morselli, C. *et al.* (2007) Oral budesonide in the treatment of chronic refractory pouchitis. *Aliment Pharmacol Ther* 25: 1231–1236.
- Greenberg, G.R., Feagan, B.G., Martin, F., Sutherland, L.R., Thomson, A.B., Williams, C.N. *et al.* (1994) Oral budesonide for active Crohn’s disease. Canadian Inflammatory Bowel Disease Group. *N Engl J Med* 331: 836–841.
- Gross, V., Bar-Meir, S., Lavy, A., Mickisch, O., Tulassay, Z., Pronai, L. *et al.* (2006) International Budesonide Foam Study Group. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Aliment Pharmacol Ther* 23: 303–312.
- Hammond, A., Andus, T., Gierend, M., Ecker, K.W., Scholmerich, J. and Herfarth, H. for the German Budesonide Foam Study Group (2004) Controlled, open, randomized multicenter trial comparing the effects of treatment on quality of life, safety and efficacy of budesonide foam and betamethasone enemas in patients with active distal ulcerative colitis. *Hepatology* 51: 1345–1349.
- Hanauer, S.B., Robinson, M., Pruitt, R., Lazenby, A.J., Persson, T., Nilsson, L.G. *et al.* (1998) Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. *Gastroenterology* 115: 525–532.
- Hellers, G., Cortot, A., Jewell, D., Leijonmarck, C.E., Löfberg, R., Malchow, H. *et al.* (1999) Oral budesonide for prevention of postsurgical recurrence in Crohn’s disease. The IOIBD Budesonide Study Group. *Gastroenterology* 116: 294–300.
- Keller, R., Stoll, R., Foerster, E.C., Gutsche, N. and Domschke, W. (1997) Oral budesonide therapy for steroid-dependent ulcerative colitis: a pilot trial. *Aliment Pharmacol Ther* 11: 1047–1052.
- Lémann, M., Galian, A., Rutgeerts, P., Van Heuverszwin, R., Cortot, A., Viteau, J.M. *et al.* (1995) Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 9: 557–562.
- Levine, A., Weizman, Z., Broide, E., Shamir, R., Shaoul, R., Pacht, A. *et al.* (2003) Israeli Pediatric Gastroenterology Association Budesonide Study Group. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 36: 248–252.
- Liacouras, C. and Ruchelli, E. (2004) Eosinophilic esophagitis. *Curr Opin Pediatr* 16: 560–566.
- Lichtenstein, G.R., Abreu, M.T. and Cohen, R., Tremaine, W., American Gastroenterological Association (2006) American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 130: 935–939.
- Lichtenstein, G.R., Bengtsson, B., Hapten-White, L. and Rutgeerts, P. (2009) Oral budesonide for maintenance of remission of Crohn’s disease: a pooled safety analysis. *Aliment Pharmacol Ther* 29: 643–653.

- Lindgren, S., Löfberg, R., Bergholm, L., Hellblom, M., Carling, L., Ung, K.A. *et al.* (2002) Effect of budesonide enema on remission and relapse rate in distal ulcerative colitis and proctitis. *Scand J Gastroenterol* 37: 705–710.
- Löfberg, R., Danielsson, A., Suhr, O., Nilsson, A., Schiöler, R., Nyberg, A. *et al.* (1996) Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology* 110: 1713–1718.
- Lundin, P.D.P., Edsbacker, S., Bergstrand, M., Ejderhamn, J., Lindanders, H., Hogberg, L. *et al.* (2003) Pharmacokinetics of budesonide controlled release capsules in children and adults with active Crohn's disease. *Aliment Pharm Ther* 17: 85–92.
- Lundin, P., Edsbacker, S., Larsson, P. and Wollmer, P. (2001) Targeted delivery of oral budesonide (entocort capsules) in healthy volunteers and Crohn's disease patients. *Gastroenterology* 120(suppl 1): A-749, 4024.
- Madisch, A., Heymer, P., Voss, C., Wiggighaus, B., Bästlein, E., Bayerdörffer, E. *et al.* (2005) Oral budesonide therapy improves quality of life in patients with collagenous colitis. *Int J Colorectal Dis* 20: 312–316.
- Mahadevan, U. and Sandborn, W.J. (2003) Diagnosis and management of pouchitis. *Gastroenterology* 124: 1636–1650.
- Mantzaris, G.J., Christidou, A., Sfakianakis, M., Roussos, A., Koilakou, S., Petraki, K. *et al.* (2009) Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. *Inflamm Bowel Dis* 15: 375–382.
- Mantzaris, G.J., Petraki, K., Sfakianakis, M., Archavlis, E., Christidou, A., Chadio-Iordanides, H. *et al.* (2003) Budesonide versus mesalamine for maintaining remission in patients refusing other immunomodulators for steroid-dependent Crohn's disease. *Clin Gastroenterol Hepatol* 1: 122–128.
- Miehke, S., Heymer, P., Bethke, B., Bästlein, E., Meier, E., Bartram, H.P. *et al.* (2002) Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicenter trial. *Gastroenterology* 123: 978–984.
- Miehke, S., Madisch, A., Bethke, B., Morgner, A., Kuhlisch, E., Henker, C. *et al.* (2008) Oral budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 131: 1510–1516.
- Miehke, S., Madisch, A., Karimi, D., Wonschik, S., Kuhlisch, E., Beckmann, R. *et al.* (2009) Budesonide is effective in treating lymphocytic colitis: a randomized double-blind placebo-controlled study. *Gastroenterology* 136: 2092–2100.
- Miehke, S., Madisch, A., Voss, C., Morgner, A., Heymer, P., Kuhlisch, E. *et al.* (2005) Long-term follow-up of collagenous colitis after induction of clinical remission with budesonide. *Aliment Pharmacol Ther* 22: 1115–1119.
- Morgan, E.T. (2001) Regulation of cytochrome p450 by inflammatory mediators: why and how? *Drug Metabolism Deposition* 29: 207–212.
- Olesen, M., Eriksson, S., Bohr, J., Jarnertot, G. and Tysk, C. (2004) Microscopic colitis: a common diarrhoeal illness. An epidemiological study in Örebro, Sweden, 1993–1998. *Gut* 53: 346–350.
- Pardi, D.S., Loftus Jr, E.V., Smyrk, T.C., Kammer, P.P., Tremaine, W.J., Schleck, C.D. *et al.* (2007) The epidemiology of microscopic colitis: a population based study in Olmsted County, Minnesota. *Gut* 56: 504–508.
- Rutgeerts, P., Löfberg, R., Malchow, H., Lamers, C., Olaison, G., Jewell, D. *et al.* (1994) A comparison of budesonide with prednisolone for active Crohn's disease. *N Engl J Med* 331: 842–845.
- Sandborn, W.J., Löfberg, R., Feagan, B.G., Hanauer, S.B., Campieri, M. and Greenberg, G.R. (2005) Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: a predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. *Am J Gastroenterol* 100: 1780–1787.
- Schoon, E.J., Bollani, S., Mills, P.R., Israeli, E., Felsenberg, D., Ljunghall, S. *et al.* (2005) Matrix Study Group. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. *Clin Gastroenterol Hepatol* 3: 113–121.
- Seow, C.H., Benchimol, E.I., Griffiths, A.M., Otley, A.R. and Steinhart, A.H. (2008) Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* CD000296.
- Teitelbaum, J.E., Fox, V.L., Twarog, F.J., Nurko, S., Antonioli, D., Gleich, G. *et al.* (2002) Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology* 122: 1216–1225.
- The Danish Budesonide Study Group (1991) Budesonide enema in distal ulcerative colitis. A randomized dose-response trial with prednisolone enema as positive control. *Scand J Gastroenterol* 26: 1225–1230.
- Thomsen, O.O., Cortot, A., Jewell, D., Wright, J.P., Winter, T., Veloso, F.T. *et al.* (1998) A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 339: 370–374.
- Travis, S.P.L., Stange, E.F., Lemann, M., Oeresland, T., Chowers, Y., Forbes, A. *et al.* (2006) NJMcM for

Visit SAGE journals online
<http://taj.sagepub.com>

SAGE JOURNALS
Online

the European Crohn's and Colitis Organisation (ECCO). *Gut* 55(suppl 1): i16–i35.

Tremaine, W.J., Hanauer, S.B., Katz, S., Winston, B.D., Levine, J.G., Persson, T. *et al.* (2002) Budesonide CIR United States Study Group. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized

placebo-controlled study in the United States. *Am J Gastroenterol* 97: 1748–1754.

Wagner, M., Lampinen, M., Sangfelt, P., Agnarsdottir, M. and Carlson, M. (2009) Budesonide treatment of patients with collagenous colitis restores normal eosinophil and T-cell activity in the colon. *Inflamm Bowel Dis* 16: 1118–1126.