CLINICAL @LERT

Budesonide led to a greater remission rate and fewer severe adverse events than did mesalamine in Crohn's disease

Thomsen OØ, Cortot A, Jewell D, et al, for the International Budesonide-Mesalamine Study Group. **A comparison of budesonide and mesalamine for active Crohn's disease.** *N Engl J Med* 1998 Aug 6;339:370-4.

Question

In patients with active Crohn's disease, is budesonide more effective and safer than mesalamine for inducing remission?

Design

Randomised, double blind, controlled trial with 16 weeks follow up.

Setting

25 centres in Denmark, France, the UK, Norway, Italy, Spain, Portugal, Greece, South Africa, Austria, Australia, and Ireland.

Patients

182 patients (68% women) who were 18-74 years of age and had Crohn's disease confined to the distal ileum, ileocaecal region, and ascending colon which was confirmed by colonoscopy, small bowel follow through, or barium enema in the previous 24 months. Exclusion criteria were Crohn's disease in the rectum; septic complications; abscess; perforation; active fistulas; ileostomy; colostomy; resection of >100 cm of the ileum; need for immediate surgery; diabetes mellitus; active peptic ulcer disease; systemic infection; clinically significant renal, hepatic, or cardiovascular disease; pregnancy; lactation; or allergy to glucocorticoids or mesalamine.

Intervention

Patients were allocated to budesonide, 9 mg once/day plus a placebo once/day (n=93), or mesalamine, 2 mg twice/day (n=89), for 16 weeks.

Main outcome measures

Remission rate. Secondary outcome measures included time to remission, changes in Crohn's Disease Activity Index score, and adverse events.

Commentary

The course of Crohn's disease is characterised by frequent flares and periods of remission. Apart from the physical suffering, patients experience many psychosocial drawbacks due to active disease, resulting in lower quality of life. Therefore it is very important to control active disease quickly, efficiently and with few side effects. The trial reported recently by Thomsen *et al* clearly shows that the topically acting glucocorticosteroid (GCS) budesonide, administered as a controlled ileal release formulation, is significantly better at inducing remission than high dose mesalamine.

The benefit is important clinically as at each time point remission rates were about 50% higher for budesonide and at 12 weeks almost twice as many patients achieved remission on budesonide (62%) compared with mesalamine (36%; $p<0.001$). The median time to remission was also shorter in the budesonide group than in the mesalamine group (28 *v* 84 days, $p=0.04$).

The remission rates obtained with budesonide are remarkably similar in all studies on the controlled ileal release capsule (CIR-Entocort). They range between 52 and 69% at eight weeks. The efficacy of

Main results

More patients in the budesonide group than in the mesalamine group were in remission after 8 weeks ($p=0.001$), 12 weeks ($p=0.004$), and 16 weeks ($p<0.001$) (table). Median time to remission was shorter in the budesonide group than in the mesalamine group (28 *v* 84 days, $p=0.04$). After 16 weeks, more patients in the budesonide group than in the mesalamine group had a decrease in the Crohn's Disease Activity Index score of ≥ 100 points or a score ≤ 150 points (71% *v* 51%, $p=0.005$). No differences between groups existed for adverse events, but fewer patients in the budesonide group than in the mesalamine group had severe adverse events (13% *v* 25%, $p=0.04$).

Conclusion

In patients with Crohn's disease, budesonide increased remission rates and reduced time to remission, Crohn's Disease Activity Index scores, and severe adverse events compared with mesalamine.

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A modified version of this abstract is also published in *ACP Journal Club*.

Remission rates for budesonide *v* mesalamine in patients with Crohn's disease

Length of follow up	Budesonide	Mesalamine	RBI* (95% CI)	NNT† (CI)
8 weeks	69%	45%	55% (19 to 107)	5 (3 to 11)
12 weeks	64%	42%	51% (13 to 105)	5 (3 to 15)
16 weeks	62%	36%	70% (24 to 139)	4 (3 to 10)

*RBI=proportional increase in rates of good outcomes between budesonide and mesalamine groups; calculated from data in article.

†NNT=number of patients who must receive budesonide to achieve 1 additional good outcome; calculated from data in article.

this regimen is slightly inferior to 40 mg prednisolone but the incidence of side effects, especially cosmetic ones like acne and moon face, is much reduced, indicating an improved efficacy:safety ratio.

A topical action of this GCS with very high activity and GCS-receptor affinity combined with high first pass metabolism is believed to be the basis of this profile. Budesonide is not the ideal treatment for active Crohn's disease. The CIR capsule is not effective in 30-40% of patients. Moreover, patients with more extensive colitis or left sided colitis will not benefit from this treatment. Attempts to develop a

colonic formulation of budesonide for the treatment of ulcerative colitis have not been successful.

There is a systemic component in the action of budesonide. In all studies with budesonide morning cortisol is suppressed and corticotropin stimulated concentrations are lower than in placebo or mesalamine treated patients. Even if only 12% of the drug reaches the systemic circulation the greatly increased receptor affinity of budesonide as well as the higher GCS anti-inflammatory activity compared with prednisolone should result in profound systemic effects. Results of ongoing studies on the effect of budesonide on bone metabolism with long term use are eagerly awaited.

Budesonide induces remission in 50–70% of the patients with active ileal or

right ileocolonic disease but in the remaining resistant patients a dose increase or a switch to prednisolone will be necessary. The side effect profile of higher doses is unknown. Moreover, budesonide does not maintain remission effectively. Long term relapse prevention with 6 mg budesonide o.m. prolonged the duration of remission in several well performed placebo controlled studies but at the end of one year the relapse rates were similar for budesonide treated patients and patients who had taken placebo.

We may conclude that it has now clearly been shown that the budesonide CIR formulation is more effective than high dose mesalamine treatment at inducing remission in active Crohn's ileitis and right sided ileocolitis. The fewer cosmetic side effects compared with

standard GCS makes its use especially attractive. Although budesonide is much more expensive than standard GCS the cost of treatment of active disease with this drug is no greater than that of the less effective high dose 5-aminosalicylic acid. The drug does not maintain remission effectively and therefore pulse therapy for each relapse is advocated. For patients experiencing two or more relapses a year immunosuppression is mandatory and because of the location of the disease, resection should also be considered.

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