Prolonged-release budesonide for mild-to-moderate ulcerative colitis

Steve Chaplin and Jonathan Digby-Bell

Cortiment is a new multi-matrix (MMX) prolonged-release formulation of budesonide for the treatment of mild-to-moderate active ulcerative colitis, which releases budesonide at a controlled rate throughout the colon. Here, Steve Chaplin outlines the clinical trial data for its efficacy and Jonathan Digby-Bell discusses its place in therapy.

**Steve Chaplin**

A topical and/or oral aminosalicylate is recommended as first-line therapy to induce remission in adults with active mild-to-moderate ulcerative colitis. Patients with a mild-to-moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis for whom a high-dose oral aminosalicylate is not sufficient may consider either a topical aminosalicylate or oral beclometasone dipropionate.

**Prolonged-release budesonide**

Cortiment is a prolonged-release formulation of budesonide licensed for induction of remission in patients with mild-to-moderate active ulcerative colitis when treatment with mesalazine is not sufficient. The gel multimatrix (MMX) tablet releases budesonide when the pH of its environment is above 7, delivering the drug throughout the colon. Other oral formulations of budesonide, Budenofalk and Entocort, are licensed only for Crohn’s disease.

**KEY POINTS**

- Cortiment is an oral prolonged-release formulation of budesonide
- It is licensed for induction of remission in patients with mild-to-moderate active ulcerative colitis when mesalazine is not sufficient
- In clinical trials, Cortiment induced remission in 17–18 per cent of patients compared with 5–7 per cent with placebo
- Efficacy was greatest in patients with left-sided disease
- Treatment was well tolerated; common adverse events included nausea and headache
- A month’s treatment with Cortiment 9mg costs £75.00

The recommended dosage is one 9mg tablet in the morning for up to eight weeks. No dose adjustment is recommended for older people but experience in this group is limited. There have been no studies in patients with impaired renal or hepatic function.

**Clinical trials**

Two clinical trials, CORE I (n=509) and CORE II (n=410), provide the key evidence for Cortiment 9mg. Both included an arm assigned to treatment with 6mg daily; these data are not described here. Patients had ulcerative colitis of at least 6 months’ duration with an Ulcerative Colitis Disease Activity Index score (UCDAI) of 4–10 points (median 6–7). About 60 per cent had previously been treated with mesalazine.

Patients were randomised to receive Cortiment or placebo or, as an active control, mesalazine 2.4g daily or Entocort (budesonide) 9mg daily. The primary endpoint was combined clinical and endoscopic remission at week 8, defined as UCDAI score ≤1, with a rectal bleeding score of 0, stool frequency score of 0, mucosal appearance score of 0 (no sign of mucosal friability on full colonoscopy).
Budesonide is a topically acting, orally administered corticosteroid with minimal systemic uptake and low bioavailability due to highly effective first-pass hepatic metabolism. Budesonide has been shown to be extremely potent (more than nine times as potent as dexamethasone) and has lower bioavailability than beclometasone. To date, most preparations of budesonide, eg Entocort and Budenofalk, have a pH-dependent action, designed to be released in the terminal ileum and proximal colon. Budesonide has been shown to be effective in inducing remission in mild to moderate ileo-colonic Crohn’s disease; however, in ulcerative colitis it is inferior to mesalazine in inducing remission. 6

Cortiment is a novel formulation of budesonide with a multimatrix (MMX) system, which releases drug at a controlled rate throughout the colon. Two well-conducted, multicentre, randomised, double-blind, placebo-controlled trials (CORE I and II) were performed to assess the efficacy of Cortiment in active ulcerative colitis. Results showed that Cortiment 9mg for eight weeks was superior to placebo in

Figure 1. Rates of combined clinical and endoscopic remission at week 8 with Cortiment 9mg and mesalazine 2.4mg in CORE I and with Cortiment 9mg and Entocort 9mg in CORE II and a ≥1-point reduction in baseline endoscopic index score.

Combined clinical and endoscopic remission was achieved in significantly more patients treated with 9mg Cortiment than with placebo (see Figure 1). Neither study was powered for a statistical comparison with the active controls, which were associated with numerically lower remission rates. Subgroup analysis showed no statistically significant differences between Cortiment and placebo in patients with proctosigmoiditis or extensive disease. In patients with left-sided disease, remission rates were 18–31 per cent with Cortiment and 6 per cent with placebo (p=0.0268 and p=0.0076). Complete symptom resolution occurred in significantly more patients treated with Cortiment (24–29 per cent vs 11–17 per cent with placebo). The rate of histological healing was significantly greater with Cortiment than with placebo in CORE II (17 vs 7 per cent) but not CORE I (4 vs 7 per cent). With the exception of histological healing in CORE I, these figures were numerically similar to those associated with Entocort and mesalazine.

Adverse effects
The frequency of treatment-related adverse events associated with Cortiment in clinical trials (26–28 per cent) was similar to that reported with placebo (24–26 per cent) and active controls (23–24 per cent). Adverse events leading to discontinuation occurred in 12–19 per cent of patients treated with Cortiment, 15–19 per cent with placebo, 11 per cent with mesalazine and 18 per cent with Entocort. Common adverse events included headache and nausea. Cortiment reduced mean morning plasma cortisol levels compared with placebo but not to a level below the normal range.

Declaration of interests
None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics
inducing clinical and endoscopic remission. There were no significant adverse effects of Cortiment including steroid-related effects.

Cortiment appears to be an effective treatment for induction of mild-to-moderate ulcerative colitis. This adds another weapon to the armoury for treating ulcerative colitis but on current evidence, it would be hard to support it as first-line therapy instead of aminosalicylates. It may be useful as:

• an alternative to aminosalicylates to induce remission in patients who are intolerant to aminosalicylates or in whom aminosalicylates are contraindicated
• to supplement aminosalicylates (as an alternative to prednisolone) to induce remission if the patient has failed to achieve remission with aminosalicylates alone in patients who are intolerant to prednisolone or in whom prednisolone is contraindicated.

Further studies are required to evaluate the effectiveness of Cortiment to induce remission compared to aminosalicylates. It would also be interesting to evaluate the effectiveness of induction of remission compared to Clipper (modified-release beclometasone), another low bioavailability corticosteroid, which has been shown to be effective in ulcerative colitis.

The results of the CONTRIBUTE study, comparing induction of remission with Cortiment to placebo in patients already taking aminosalicylates, is anticipated in the near future, which will add to our understanding of the place of Cortiment in treatment algorithms.

Declaration of interests
None to declare.

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References

POEMs

Some benefit to treating mild hypertension to prevent stroke, cardiovascular deaths and overall mortality

Clinical question: What are the benefits of treating mild hypertension?

Bottom line: Treating mild hypertension over five years decreases the risk of stroke, cardiovascular death, and overall mortality in a small proportion of patients. The numbers needed to treat (NNT) — the numbers of patients who need to be treated to prevent one additional outcome from occurring — are below. Pay attention to the confidence intervals (CIs), which tell us the best case/worst case possibilities. Also note that some of these intervals are very large, meaning that we cannot place much confidence in the reported NNT. (LOE = 1a)


Synopsis: The authors used the literature search results of a previous Cochrane meta-analysis and updated it by searching several databases. They included studies that lasted at least one year and evaluated treatment of grade 1 hypertension (range 140/90mmHg to 159/99mmHg) in patients with no previous cardiac disease. They were able to use individual patient data (instead of comparing only the results across studies) for a total of 15 266 patients. The risk of bias in the studies was low. The research included single drug treatment and stepped-care approaches.

Over an average five years of treatment, there was no significant decrease in overall cardiovascular events, coronary events, or, predictably, heart failure. The likelihood of a stroke, death due to a cardiovascular event, or all-cause mortality was lower with treatment (see below). Overall, 5.6 per cent of patients withdrew from treatment because of adverse effects (number needed to treat to harm = 36, 95% CI 23–75).

NNT for five years (95% CI):
• Stroke: 173 (108–810)
• Cardiovascular death: 95 (55–1188)
• Overall mortality: 99 (66–273)
• Heart failure: not significant
• Coronary events: not significant.