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Alimentary Tract

Beclomethasone dipropionate in Crohn's ileitis: A randomised, double-blind trial

Cosimo Prantera[a,*], Marina Rizzi[a], Mario Cottone[b], Angelo Casa[b], Vito Annese[c], Giacomo Carlo Sturniolo[d], Stefano Marconi[e], Herbert Lochs[f]

[a] Azienda Ospedaliera San Camillo Forlanini, Rome, Italy
[b] Division of Internal Medicine, Department of General Medicine and Pneumology, University of Palermo. "V. Cervello Hospital", Palermo, Italy
[c] Dipartimento Oncologico AOU Careggi, Florence, Italy
[d] Department of Surgical and Gastroenterological Sciences, University of Padova, Padua, Italy
[e] Medical Department Chiesi Farmaceutici S.p.A., Parma, Italy
[f] University of Innsbruck, Innsbruck, Austria

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ABSTRACT

Background: Steroids, the mainstay of Crohn's disease treatment, have been associated with systemic side effects.
Aim: To evaluate the efficacy and tolerability of beclomethasone dipropionate for maintaining remission induced by a short course of systemic steroids in patients with Crohn's ileitis with or without right colonic involvement.
Methods: Patients ($n = 84$) with active Crohn's disease who achieved remission during a 2-week prednisone run-in period were randomised to receive beclomethasone dipropionate for 24 weeks or continue prednisone for a further 2 weeks followed by placebo for 22 weeks. The primary outcome was relapse rate (Crohn's Disease Activity Index score > 150 and an increase of ≥60 points from baseline) or withdrawal due to disease deterioration.
Results: The relapse rate was 23.3% and 53.8% in beclomethasone dipropionate and placebo groups, respectively ($p = 0.027$). According to Kaplan–Meier analysis, the cumulative relapse rate was 38.0% in the beclomethasone dipropionate group and 56.0% in the placebo group ($p = 0.025$). Six percent and 1.7% of all adverse events in the beclomethasone dipropionate and placebo groups, respectively, were endocrine-related.
Conclusion: These results demonstrate that beclomethasone dipropionate significantly reduces the relapse rate in post-active Crohn's ileitis patients compared with placebo after induction of remission with a short course of systemic steroids, and is well tolerated.

1. Introduction

Systemic steroids are the standard treatment for Crohn's disease (CD). They induce rapid symptom remission, allowing patients to return to their normal daily activities in a short time frame. The American Gastroenterology Association [1], British guidelines [2] and the European Crohn's and Colitis Organization (ECCO) Consensus [3] recommend the use of systemic steroids as first-line therapy for the management of moderate-to-severely active CD.

The National Cooperative Crohn's Disease Study (NCCDS) demonstrated that the use of steroids in the treatment of CD has been associated with a good clinical response, with 60% of prednisone-treated patients achieving remission during 17 weeks of therapy [4]. A 92% remission rate within 7 weeks in patients treated with prednisolone 1 mg/kg/day was reported in another study [5].

Serious problems, however, limit steroid use; side effects associated with their long-term use are severe [6], and patients may develop steroid-dependent disease [7]. Therefore, it would seem advisable to administer them for only a short period of time [7], but steroid clinical trial data and clinical practice experience both suggest that short-term treatment is followed by a rapid symptom relapse [7]. Steroids, therefore, have no role in maintenance treatment [2].

Oral steroid preparations with a lower incidence of systemic side effects have been in development for a number of years. These agents have produced promising results in terms of efficacy and safety [8]. Maintenance therapy with a controlled ileal release preparation of budesonide, a steroid specifically formulated for use in patients with ileal or ileo-colonic CD, has been shown to prolong time to relapse after achievement of remission [9,10]. However,

* Corresponding author at: Azienda Ospedaliera San Camillo-Forlanini, Circonvallazione Gianicolense 87, Roma, Italy. Tel.: +39 0658703369; fax: +39 065562249.
E-mail address: prantera@tin.it (C. Prantera).

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budesonide failed to demonstrate a clear difference when compared with placebo in maintaining remission [11].

Beclomethasone dipropionate (BDP) is a glucocorticosteroid that demonstrates rapid, potent anti-inflammatory properties and is associated with fewer side effects than traditional systemic steroids [12,13]. BDP displays little systemic activity after oral or rectal administration, and efficacy similar to that of prednisolone in the enema form [12]. In three studies of 4-week duration, in which doses of BDP of up to 10 mg/day were administered to patients with ulcerative colitis, mean plasma cortisol levels were reduced without any adverse clinical sequelae [13–15]. In a retrospective study in 40 patients with CD treated for 24 weeks with doses of between 5 and 10 mg/day, only three mild BDP-related side effects were observed [16].

BDP in its oral formulation has modified-release core and a gastro-resistant film coating (BDP-coated tablets) that prevents the tablets from dissolving in the upper GI tract, ensuring that the active ingredient is released in the distal small bowel and throughout the colon [17].

The objective of the study was to explore whether patients with Crohn's ileitis with or without right colon involvement, who received a 2-week course of prednisone followed by 24-week treatment with BDP-coated tablets, maintained their remission at 6 months, as compared with a 4-week course of systemic prednisone followed by placebo. The safety profile of this treatment was also assessed.

2. Materials and methods

2.1. Study design

This was a randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multicentre study with a 2-week open-label run-in period (study registration number MC/PR/1405/002/02; the full study protocol is accessible at Osservatorio Nazionale sulla Sperimentazione Clinica dei Farmaci, http://oss-sper-clin.agenziafarmaco.it/). All patients received systemic steroids (prednisone) at a dose of 60 mg/day in the first week of the run-in period, and at a dose of 30 mg/day in the second week. Patients who achieved remission (Crohn's Disease Activity Index (CDAI) $\leq$ 150) during the run-in period, according to investigators of each centre, were then randomised in a 1:1 ratio to the BDP or placebo groups. The randomisation list, generated by a computer, was composed of four-element blocks balanced by treatment and was kept sealed until the trial was completed. In the BDP group, patients received BDP 15 mg/day for 2 weeks and, subsequently, BDP 10 mg/day for 22 weeks. The placebo group continued prednisone for a further 2 weeks after run-in (15 mg/day for 7 days; 5 mg/day until day 14), plus identical BDP placebo for the entire study period. In order to maintain the double-dummy condition, during weeks 1 and 2, the supply for that period was provided in indistinguishable capsules.

2.2. Study participants

Patients with active CD (aged $\geq$18 years) were enrolled in 21 specialised centres, in five different countries (eight in Italy, two in Germany, one in Switzerland, two in Hungary and eight in Romania). Active CD was defined as a CDAI score of 180–400. Patients had CD confined to the distal ileum, ileocaecal region and/or ascending colon, as verified by colonoscopy or X-ray not more than 6 months prior to randomisation. Exclusion criteria were CD involving only the colon, perianal CD, septic complications, abscesses, perforation or active fistulae. Other exclusion criteria were ileostomy, previous resection of the ileum of >100 cm, treatment with anti-tumour necrosis factor (TNF) agents within the preceding 6 months and steroids or immunosuppressors. Patients with signs or symptoms of severe, progressive or uncontrolled renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurological or cerebral disease were also excluded.

The study was approved by the local ethics committees and conducted in compliance with the Helsinki Declaration and all International Conference on Harmonization Good Clinical Practice Guidelines. Written informed consent was obtained from each patient prior to the study.

2.3. Study drugs

BDP 5 mg, prednisone 5 mg and matching placebo tablets were supplied by Chiesi Farmaceutici S.p.A. (Parma, Italy). BDP, prednisone and placebo were provided as identical capsules. Any therapy for CD was interrupted at screening visit, and no other treatment for active CD was allowed during the study.

2.4. Clinical and laboratory assessments

After the screening visit, patients were assessed on six separate occasions: at the end of the run-in period (i.e. at randomisation/baseline), and then after 2, 4, 8, 12 and 24 weeks (or at early withdrawal). The patient's clinical condition, which was assessed by physical examination and vital signs, and haematocrit levels were assessed at each visit, and their CDAI score was calculated. Patients were also given a diary card for their CDAI calculation. Drug compliance assessed by a tablet count was also recorded at each visit. All other laboratory tests (and assessing adverse events) were performed at screening, randomisation and at end of the study (week 24, or earlier for patients who withdrew early from the study). Plasma cortisol levels were assessed at randomisation, at study end and in the case of withdrawal for any reason.

The primary outcome measure was relapse rate. Relapse was defined as a CDAI score of >150 and an increase of $\geq$60 points from the value at baseline (in order to be more stringent in the definition of relapse, with respect to definitions more commonly adopted [increase in CDAI $\geq$70 or $\geq$100 from baseline]), or withdrawal due to disease deterioration. Secondary endpoints included efficacy of BDP with respect to CDAI, time to relapse and safety profile.

2.5. Safety assessments

The number of patients who reported any adverse events (AEs), and the type and severity of the AEs, were summarised and analysed for their possible relationship to the study drugs. The safety population was composed of any patient randomised to treatment who had received at least one dose of the study drug.

2.6. Statistical analyses

The sample size was calculated based on the assumption that a difference of at least 20% in the primary variable should be observed between the two groups. It was estimated that 102 patients per group would need to be evaluated in order to detect a 20% difference in relapse rate with 80% power at a level of 0.05, assuming a relapse rate of 29% with BDP treatment. Thus, the plan was to enrol 320 patients with active CD to achieve a sample size of 256 randomised patients, approximately 12–16 patients per centre.

Baseline characteristics (e.g. age, sex, history of CD, medical history and previous treatment) were summarised by descriptive statistics. Relapse rate was analysed in the per protocol population (PP). PP was defined as all randomised patients of intention-to-treat (ITT) population who were evaluable for the primary endpoint, excluding the major protocol violations. The ITT population was