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Alimentary Tract

Collagenous colitis: Requirement for high-dose budesonide as maintenance treatment

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ABSTRACT

Background: Controlled studies show high efficacy of budesonide in inducing short-term clinical remission in collagenous colitis (CC), but relapses are common after its withdrawal.
Aim: To evaluate the need for high-dose budesonide (≥6 mg/d) to maintain clinical remission in CC.
Methods: Analysis of a multicentre retrospective cohort of 75 patients with CC (62.3 ± 1.5 years; 85% women) treated with budesonide in a clinical practice setting between 2013 and 2015. Frequency of budesonide (9 mg/d) refractoriness and safety, and the need for high-dose budesonide to maintain clinical remission, were evaluated. Drugs used as budesonide-sparing, including azathioprine and mercaptopurine, were recorded. Logistic regression analysis was performed to evaluate the risk factors associated with the need for high-dose budesonide (≥6 mg/d) to maintain clinical remission.
Results: Budesonide induced clinical remission in 92% of patients, with good tolerance. Fourteen of 68 patients (21%; 95% CI, 13–32%) needed high-dose budesonide to maintain remission. Only intake of NSAIDs at diagnosis (OR, 8.6; 95% CI, 1.6–44) was associated with the need for high-dose budesonide in the multivariate analysis.
Treatment: with thiopurines was effective in 5 out of 6 patients (83%; 95% CI, 44–97%), allowing for withdrawal from or a dose decrease of budesonide.
Conclusions: One fifth of CC patients, especially those with NSAID intake at diagnosis, require high-dose budesonide (≥6 mg/d) to maintain clinical remission. In this setting, thiopurines might be effective as budesonide-sparing drugs.

1. Introduction

Microscopic colitis (MC) is a generic term that includes two main forms, collagenous colitis (CC) and lymphocytic colitis (LC). The term represents a form of inflammatory bowel disease characterized by the triad of non-bloody chronic or relapsing watery diarrhoea, macroscopically normal or mildly abnormal colonic

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mucosa in colonoscopy, and characteristic histopathological findings [1].

Recent meta-analysis of randomized clinical trials concluded that oral budesonide is the drug of choice for inducing clinical remission in patients with CC [1,2]. Also, meta-analysis of the three randomized controlled trials (RCTs) evaluating maintenance therapy of CC concluded that oral budesonide (at a dose of 4.5–6 mg/d, for 6–12 months) is effective in maintaining clinical remission in patients with CC [1]. However, the clinical relapse rate after treatment discontinuation was very high (76–82%). Thus, 'European Microscopic Colitis Group' (EMCG) guidelines recommend using low-dose budesonide (up to 6 mg/d) to maintain clinical remission [3]. However, the percentage of patients requiring high-dose budesonide (6 mg/d or more) to maintain clinical remission is unknown. The most effective and safe maintenance treatment in MC patients with a chronic, active course also remains unknown. The 6 mg daily budesonide dose used in several trials is probably too high for long-term treatment in most elderly people [3].

Oral budesonide administration in CC is considered to be safe, but there are insufficient data on long-term adverse events [1–3]. Available data on the safety of medium- and long-term treatment with budesonide are derived from studies performed in other diseases such as Crohn's disease and primary biliary cirrhosis. In fact, patients with Crohn's disease receiving 6 mg daily of budesonide for extended periods of time experienced a higher rate of treatment-related adverse events as compared with placebo, although these events did not result in study withdrawal and therefore must have been relatively mild [4]. Among these, mild reductions in bone mineral density have been described with budesonide use. A mean budesonide dose of 8.5 mg/day (range, 6–9 mg/day) for 2 years induced more alterations in bone mineral density (loss >2% per year) than no treatment with corticosteroids in patients with Crohn's disease in remission [5]. However, in a recent case-control study, treatment with budesonide at a dose of around 3 mg/day was not associated with an increased fracture risk [6]. Nevertheless, it may not be extrapolated that higher doses are safe in terms of fractures. In this sense, oral budesonide (6 mg/d for three years) associated with ursodeoxycholic acid to treat primary biliary cirrhosis patients was also associated with a decrease in bone mass density, unrelated to the stage of liver disease [7]. Further information on the long-term effects of oral budesonide on bone mineral density in CC patients would be beneficial.

Conversely, using oral budesonide for extended periods of time in Crohn's disease patients seems to be associated with the risk of adrenocorticoid suppression [4]. There does appear to be a dose-dependent suppression of the adrenocortical axis, with those patients receiving 6 mg numerically more likely to have an abnormal ACTH stimulation test than those receiving 3 mg daily [4].

The aim, then, of the present study was to evaluate the need for high-dose budesonide (≥6 mg/d) to maintain clinical remission in CC.

2. Patients and methods

2.1. Patients

Patients with CC treated with budesonide for active disease between 2013 and 2015 in ten Spanish hospitals were retrospectively reviewed. Those fulfilling the following inclusion criteria were included: (1) treatment with budesonide according to the EMCG algorithm [3]; (2) number of stools and liquid movements noted at each visit in the patient's medical chart; and (3) follow-up in all cases for at least 12 months. The EMCG algorithm consists of: (1) induction of remission with oral budesonide 9 mg/day for 4–6 weeks; (2) maintenance therapy with the minimum dose of budesonide needed to maintain remission, i.e., 1.5–6 mg/d (the dose of 1.5 mg/d, corresponding to 3 mg every other day); (3) after 3–6 months of maintenance therapy, budesonide withdrawal or not based on the decision of the physician in charge; and (4) in case of relapse after withdrawal, budesonide reintroduced at the lowest effective dose to maintain clinical remission.

Demographic data, clinical and histological data at diagnosis, smoking status, presence of concomitant diseases, use of drugs known to be associated with MC, and response to treatment were recorded in a structured database. Current medication use was defined as the continuous or frequent (> 3 d weekly) use of a medication for >2 weeks, at the time of diagnosis. Therapy in those patients requiring high-dose budesonide (≥6 mg/d) was recorded.

2.2. Diagnostic criteria for CC

The diagnosis of CC was based on both clinical and histological criteria, as previously described [1]. The clinical criteria were chronic watery diarrhoea of at least 1 month's duration and a grossly normal appearance of colonic mucosa on colonoscopy. The histological criteria were (1) presence of an abnormal surface subepithelial collagen layer with a thickness ≥10 μm, entrapping superficial capillaries, and with an irregular lacy appearance on the lower edge; (2) increased chronic inflammatory infiltrate (plasma cells and lymphocytes) in the lamina propria; (3) increased numbers of surface intra-epithelial lymphocytes (normal <5 per 100 epithelial cells); and (4) damage to surface epithelium, with flattening of epithelial cells and/or epithelial loss and detachment, and minimal crypt architecture distortion.

2.3. Definition of active disease and remission

According to the Hjortswang criteria, patients with an average of ≥3 faeces/day or ≥1 liquid deposition/day in one week are considered as presenting clinically active disease [8]. In this sense, and taking into account the retrospective nature of the study, clinical remission was considered as a clear reduction of daily stool number, with no or infrequent liquid stools and urgency.

2.4. Ethical approval

The ethical and research committees of all participating hospitals approved the research protocol.

2.5. Statistical methods

Results are expressed as mean ± SEM, or as median and the interquartile range (IQ) as required, for quantitative variables, or as percentage and its 95% confidence interval (CI) for qualitative variables. Chi square statistics were used to compare qualitative variables. Student-t-test and Mann–Whitney test were used for parametric and non-parametric quantitative variables, respectively.

A logistic regression analysis was performed to evaluate the risk factors associated with the need for high dose budesonide (≥6 mg/d) to maintain clinical remission. Those variables with a significant association in the univariate analyses ($p < 0.05$) were included in the model, using a stepwise method of introduction. The odds ratio (OR) and its 95% CI were calculated to assess the strength of each significant association. Statistical significance was predetermined as $p < 0.05$.

3. Results

In the 2013–2015 study period, 158 patients with CC were diagnosed in the participating hospitals. The flow of patients during the