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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

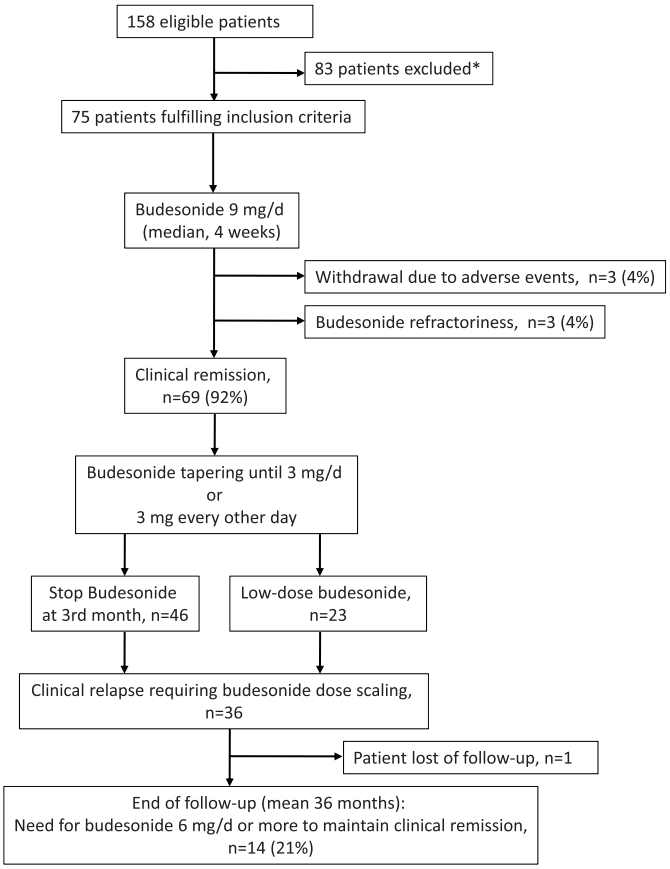

Fig. 1. Flow of patients during the study.
*Reasons for exclusion (n = 83): -Loss of follow-up (n = 9); -Lack of adherence to EMCG rules when using budesonide (n = 6); -Lack of enough data (n = 17); -Use of loperamide, mesalazine or cholestyramine to induce remission (n = 11); -Spontaneous remission (n = 28); -Remission induced by medication withdrawal (n = 12).

study is described in Fig. 1. Seventy-five of them met the inclusion criteria (62 ± 1.5 years; 85% women). Their clinical characteristics at diagnosis are presented in Table 1. The reasons for exclusion of the rest of the patients were multiple, including loss of follow-up (n = 9), lack of adherence to the EMCG guidelines when using budesonide (n = 6), lack of recording of number of stools and liquid movements (n = 17), use of other drugs to induce remission such as loperamide, mesalazine and/or cholestyramine (n = 11), and spontaneous remission (n = 28) or remission induced by medication withdrawal (n = 12).

With respect to the concomitant use of drugs, non-steroidal anti-inflammatory drugs (NSAIDs) were discontinued after CC diagnosis in 8 out of 12 patients, proton-pump inhibitors (PPIs) were discontinued in 2 out of 27 patients (mainly taking omeprazole), and serotonin-specific reuptake inhibitors (SSRIs) in 2 out of 20 patients. In all cases in which these drugs were discontinued diarrhea persisted and budesonide therapy was started.

Table 1
Clinical characteristics of included patients at diagnosis (N = 75).

Variable	
Age (years) (mean ± SEM)	62 ± 1.5
Sex (% female)	85%
Daily watery stool number (median and IQ)	5 (3–7)
Diarrhoea duration (months) (median and IQ)	12 (3–33)
Autoimmune associated diseases (%)	27% Polyarthritis (3); Thyroiditis (9); Other (8)
Smoking (active/Ex/Never) (%)	21.5%/5.5%/73%
Intake of NSAIDs/PPIs/SSRIs (%)	20.5%/38%/28%

NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton-pump inhibitors, SSRIs, selective serotonin reuptake inhibitors.

3.1. Response to budesonide

Budesonide 9 mg/d was administered for a median period of 4 weeks (IQ, 4–6). Sixty-nine of the 75 patients (92%; 95% CI, 84–96%) achieved clinical remission. Daily watery stool number decreased from 6.9 ± 1.06 to 0.11 ± 0.04 ($p < 0.001$). Budesonide intolerance was observed in 7 patients, requiring withdrawal in 3 of them (4%) (1 with palpitations and general poor condition, 1 with steroid myopathy, and 1 with a hypertensive crisis and mouth sores). In 3 patients (4%) budesonide refractoriness was observed.

3.2. Maintenance of remission

As mentioned, budesonide was tapered below 6 mg/d, until either achieving the lowest possible dose or withdrawal. Decision on withdrawal depended on the physician in charge; budesonide was withdrawn in 67% of patients after at least 3 months of therapy. During follow-up (mean, 36 ± 2.9 months), 53% of patients had at least 1 clinical relapse, and 40% two or more relapses, while attempting budesonide withdrawal. In all these cases, budesonide dose was scaled using the previous effective dose or reintroduced (9 mg/day) with a posterior new tapering to the lower effective dose. Finally, 14 of 68 patients achieving initial clinical remission with budesonide (one patient was lost at follow-up) (21%; 95% CI, 13–32%) needed high-dose budesonide (≥6 mg/d) to maintain clinical remission. In the rest of relapsing cases, low-dose budesonide (i.e., either 3 mg daily or 3 mg every other day) was useful to maintain long-term clinical remission.

3.3. Risk factors in the need for high-dose budesonide to maintain clinical remission

Diarrhoea duration (24 *vs.* >24 months) and intake of either serotonin-specific reuptake inhibitors (SSRIs) or nonsteroidal anti-inflammatory drugs (NSAIDs) were associated with the need for high-dose budesonide in the univariate analysis. However, only NSAID use at diagnosis showed an independent association (OR, 8.5; 95% CI, 1.6–44).

The clinical characteristics of included patients according to the use of NSAIDs at diagnosis are presented in Table 2. Patients on NSAIDs at diagnosis had polyarthritis more often than those not taking these drugs (17 *vs.* 2%; $p = 0.024$). Frequency of clinical relapse in patients taking NSAIDs at diagnosis after budesonide tapering <6 mg/d was 80%, whereas it was 40% in patients not taking NSAIDs ($p = 0.006$). In the same sense, the need for high-dose budesonide to maintain clinical remission was 45% *vs.* 10% in patients taking and not taking NSAIDs at diagnosis, respectively ($p = 0.011$).

Table 2
Clinical characteristics of patients starting maintenance treatment with budesonide according to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) at diagnosis.

NSAIDs	Yes (n = 12)	No (n = 56)	p
Sex (% female)	92%	84%	0.50
Age (years)	68 ± 3	61 ± 1.8	0.12
Diarrhoea duration (months)[a]	9.5 (4–45)	11 (3–30)	0.78
Daily watery stool number[a]	5.5 (3–9)	5 (3–6)	0.32
Smoking (% Active + Ex) (Active/Ex/Never)	100% (2/10/0)	91% (12/38/4)	0.53
Polyarthritis (%)	17%	2%	0.024

[a] Median and interquartile range.

3.4. Treatment of patients with budesonide-refractoriness or budesonide-dependence

As previously mentioned, there were 3 budesonide-intolerant patients from whom budesonide was withdrawn, 3 budesonide-refractory patients, and 14 patients with budesonide dependence on doses ≥6 mg/d.

The physicians in charge decided to start azathioprine in 6 patients (mean age, 57 ± 5.9 years; 100% women), 1 with budesonide refractoriness, 2 with budesonide intolerance, and 3 with budesonide dependence. Azathioprine was administered at a mean dose of 2.2 ± 0.2 mg/kg/d. There was a response in 4 patients, with budesonide withdrawal in 3 and tapering to 3 mg/d in 1. In 1 additional patient, azathioprine was stopped due to dyspepsia, and mercaptopurine was started with success, achieving budesonide withdrawal. Thus, thiopurine efficacy was achieved in 5 of 6 patients (83%; 95% CI, 44–97%). In the patient with no response, azathioprine was stopped because of severe leucopenia.

The remaining 14 patients underwent different therapeutic strategies. On one hand, 7 patients were maintained in remission with high dose budesonide (6 mg/day). On the other hand, 2 patients were treated with budesonide 3 mg/day *plus* loperamide, and 5 patients from whom budesonide was withdrawn were treated with either loperamide on demand (3 patients; in two of them previously requiring NSAIDs, these drugs were definitively stopped), mesalazine (1 patient), or cholestyramine (1 patient with associated bile acid malabsorption). The response to these treatments was variable, with episodic watery diarrhoea persisting in some of them.

4. Discussion

Budesonide is highly effective in inducing clinical remission in CC, but relapses are frequent after treatment withdrawal [1–3]. In the present series of patients treated in a clinical practice setting, budesonide induced clinical remission in 92% of patients, being the relapse rate when doses were tapered of 53% (lower than the percentage of 70–80% described in clinical trials, since in only 67% of patients had budesonide been tapered until complete withdrawal).

In view of the high relapse rate after withdrawal, it has been proposed to use low doses of budesonide in order to maintain remission [3]. This strategy has shown to be highly effective, maintaining clinical remission in 65%–80% of patients, with budesonide doses of 4.5–6 mg/d for 6–12 months [1]. However, budesonide withdrawal at this moment is also associated with a high relapse rate, of 70–80%. Thus, the EMCG recommended maintaining remission with the lowest possible dose of budesonide (i.e., up to 3 mg every other day) [3]. However, this strategy has not been validated in clinical trials, and the percentage of patients who cannot decrease the dose below 6 mg/d is unknown. Of note, results of the present study show that 21% of patients required a dose of budesonide ≥6 mg/d to maintain clinical remission in a clinical practice setting. As mentioned in the introduction, this dose may induce a decrease in bone mineral density and may also suppress the adrenocortical axis. Thus, long-term use of budesonide ≥6 mg/d may not be exempt from adverse events, mainly in aged people like patients with CC. Therefore, alternative treatments for this clinical situation will be welcomed.

There are scarce data suggesting a role for thiopurines in the treatment of budesonide-dependent and budesonide-refractory patients with CC [9–11]. Mention should be made of a retrospective case series including 46 patients with MC (32 with CC) who were corticosteroid-dependent or did not tolerate corticosteroids [11]. In this study, 13 of the patients (28%) showed a long-term clinical response to azathioprine. Thirty-one patients experienced intolerance (67%), and in two cases the thiopurine drug proved ineffective (4%). Thirteen of the 31 patients that did not tolerate azathioprine were switched to mercaptopurine, achieving clinical remission in 6 cases (46%). The overall thiopurine response rate in this study was therefore 41%. On the basis of these results, a recent evidence-based review concluded that thiopurines may be effective in patients with MC who are corticosteroid-dependent or who fail to respond to corticosteroids. The degree of recommendation was weakly in favor, considering that thiopurines are drugs with a relevant incidence of adverse effects [1]. Results of the present study are in agreement with this recommendation. In a patient with indication for thiopurine use we need to counterbalance efficacy and adverse events, but also severity of diarrhoea, patient quality of life, age, and concomitant morbidity. In this sense, in the present study the physicians in charge indicated azathioprine use in only 30% of the candidate patients. When thiopurines were used their efficacy seemed to be good, with a response in 83% of patients; although the sample size was small these observations reinforce the above-mentioned statement. Further prospective multicentre studies are required to increase the level of recommendation. It has to be taken into account that in these cases other possible therapeutic alternatives to budesonide and thiopurines exist, but the evidence in favor of their use is scant [1]. In this sense, evidence suggests that mesalazine is not a good drug to induce clinical remission, but there are no data on its effectiveness to maintain remission. Data on the use of cholestyramine mainly in CC patients with concomitant bile acid malabsorption exists, but their scientific quality is low. The use of loperamide is suggested in cases of mild CC, since it reduces the frequency of stools and the incontinence, thereby improving patient health-related quality of life. Finally, concomitant medications used by the patient have to be reviewed, and drugs associated with CC should be withdrawn if possible.

NSAID use has been associated in several studies with the risk of developing CC [12–15]. A recent paper suggested that current exposure to NSAIDs and prolonged use for 4–12 months increase the risk of MC, mainly if patients are also taking proton-pump inhibitors [15]. In addition, current use of NSAIDs has been included as an independent variable in a scoring system to predict microscopic colitis in patients with chronic diarrhoea [16]. Treatment of CC implies stopping the use of NSAIDs if possible, but there are no good alternatives to these drugs, and patients often restart them out of need. To our knowledge, this is the first time that NSAID exposure has been related with the clinical course of the disease, disclosing an independent association with an increased relapse rate and the need for high doses of budesonide to maintain clinical remission. The possible mechanisms by which NSAIDs could induce intestinal damage have recently been reviewed [15]. Alterations in colon mucosal barrier, increase in gut permeability, and interactions with bile salt inducing cytotoxicity have been implicated, and the dysbiosis induced by the concomitant use of PPIs could play a role. On the basis of the present results, there is the need for further clarifying whether CC patients requiring concomitant use of NSAIDs should be treated with a more intensive course of budesonide, using high doses (≥6 mg/d) to maintain remission.

The present study has some limitations due to the retrospective nature of the data collection. However, all included CC patients were treated according to the EMCG algorithm, which allowed a homogeneous treatment protocol and correct recording of study variables.

In conclusion, around 20% of CC patients require high-dose budesonide (≥6 mg/d) to maintain clinical remission; this dose should be probably considered too high for long-term treatment in most of elderly people. In this setting, thiopurine arise as effective budesonide-sparing drugs. However, some reluctance to use thiopurines in CC patients is documented, which indicates the need for further treatments options with a safer profile. NSAID use at diag-

nosis is associated with a relapsing clinical course and the need for high doses of budesonide to maintain remission.

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Conflict of interest

None declared.

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