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Budesonide Maintenance in Microscopic Colitis: Clinical Outcomes and Safety Profile from a Population-Based Study

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Abstract

BACKGROUND: Outcomes and safety of budesonide maintenance therapy in microscopic colitis (MC) are not well known.

METHODS: Adult residents of Olmsted County, Minnesota diagnosed with MC (2002–2019) and treated with budesonide were identified using the Rochester Epidemiology Project. Response was assessed at 12 +/− 4 weeks after initiation of therapy and defined as complete (resolution of diarrhea), partial (50% improvement in number of bowel movements), nonresponse (<50% improvement), and intolerance (discontinued due to side-effects). For safety outcomes, cases (budesonide maintenance) and MC controls (no budesonide therapy) were matched by gender and age at diagnosis (+/−2 years).

RESULTS: A total of 450 patients were identified, of which 162 (36.0%) were treated with budesonide for induction of clinical remission [median age 67 (23–91) years and 126 (77.8%) female]. Clinical outcomes for induction were as follows: 130 (80.2%) complete response, 22 (13.6%) partial response, 8 (4.9%) no response, and 2 (1.2%) intolerance. After induction, 96 (63.2%) had recurrence after discontinuation; 27 (28.1%) required further budesonide induction treatment without maintenance, 56 (58.3%) required long-term budesonide maintenance, and 13 (13.5%) were treated with other therapies. Of those receiving budesonide maintenance, all responded [55 (98.2%) complete, 1 (1.8%) partial]. No patient stopped maintenance from adverse events. The median duration of follow-up was 5.6 years (0.3–18.9). There was no significant difference between cases and controls in the incidence of osteopenia/ osteoporosis, diabetes mellitus, hypertension, glaucoma, or cataracts.

CONCLUSION: The long-term use of budesonide in MC appears to be effective and generally well tolerated with limited adverse effects.

Keywords

microscopic colitis; budesonide; maintenance; collagenous colitis; lymphocytic colitis

Introduction

Microscopic colitis (MC) is a common cause of chronic diarrhea and is comprised of two subtypes, lymphocytic colitis (LC) and collagenous colitis (CC) distinguished by their histological findings.[1] The American Gastroenterological Association recommends budesonide as first-line therapy in those with moderate-severe symptoms.[2] However, after discontinuation of budesonide, relapse is common, ranging from 40–81%, requiring many patients to remain on maintenance therapy.[3–4]. The lowest possible dose that maintains remission is typically used in patients requiring long-term budesonide therapy.

Potential adverse effects associated with systemic corticosteroids include metabolic bone disease, hypertension, hyperglycemia, as well as ophthalmologic disorders such as glaucoma and cataracts. Budesonide is preferred to systemic corticosteroids, such as prednisone, due to a lower risk of side effects due to its high first-pass metabolism. However, there are limited data evaluating the tolerability and long-term safety of budesonide in MC. We performed a population-based study on the use of budesonide in MC for maintenance to assess treatment outcomes and adverse events.

Methods

The Rochester Epidemiology Project (REP) is a medical records linkage system containing longitudinal medical data on all medical encounters for residents of Olmsted County, Minnesota.[5–9] Mayo Clinic and Olmsted County Medical Center are the two main health systems for Olmsted County. Residents age 18 years diagnosed with MC between January 1, 2002 through December 31, 2019 were identified based on pathology reports using the REP and confirmed by chart review. Patients with at least 4 months of follow up were included, and those with inflammatory bowel disease before or after MC diagnosis were excluded.

Data was collected on MC subtype (LC or CC), age, body mass index, smoking status (never, former, current), presence of other medical conditions (hypertension, diabetes mellitus, osteopenia/osteoporosis, cataracts, glaucoma) at diagnosis, treatment with budesonide (induction and maintenance), treatment with concomitant medications for MC (loperamide, bismuth subsalicylate, bile acid sequestrant, mesalamine), budesonide treatment response (complete, partial, nonresponse, intolerance), concurrent use of CYP3A4-inhibitors (strong, moderate) with budesonide,[10–11] and safety outcomes (new diagnosis or worsening of hypertension, diabetes mellitus, osteopenia/osteoporosis, cataracts, glaucoma) during and within 12 months of completing budesonide maintenance therapy.

Cases were MC patients that received budesonide maintenance therapy while controls were MC patients not treated with budesonide or other corticosteroids. Cases and controls were

matched 1:1 by gender and age at MC diagnosis (+/−2 years) to evaluate safety outcomes, as above, during and within 12 months of completing budesonide maintenance therapy or within 12 months of MC diagnosis, respectively.

Treatment response for those on budesonide was assessed at 12 +/− 4 weeks after initiation of therapy and defined *a priori* as complete (resolution of diarrhea), partial (50% improvement in number of bowel movements), nonresponse (<50% improvement), and intolerance (budesonide discontinued due to side-effects). Recurrence was defined as new diarrhea (3 bowel movements per day) after initial symptom improvement and lack of other causes of diarrhea. Duration of follow-up was determined from date of MC diagnosis to date of last clinic visit.

Continuous variables were reported as means with standard deviation (SD) and categorical variables as median (range) or frequency (percentages). Data analysis was performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC) and R version 3.6.2. This study was approved by Mayo Clinic and Olmsted Medical Center institutional review boards.

Results

There were 450 patients diagnosed with MC between 2002–2019 in Olmsted County, of which 162 (36.0%) were treated with budesonide [median age 67 years (23–91); 126 (77.8%) female] (Figure 1). Clinical characteristics are displayed in Table 1 with no significant differences between MC subtypes. Budesonide was initial therapy in 55/162 (33.9%) patients while 107/162 (66.1%) had failed another medication or combination of medications prior to budesonide initiation, including loperamide 88/107 (82.2%), bismuth subsalicylate 46/107 (43.0%), bile acid sequestrant 9/107 (8.4%), and mesalamine 5/107 (4.7%).

All 162 patients received budesonide for induction of clinical remission, of which 130 (80.2%) had complete response, 22 (13.6%) partial response, 8 (4.9%) no response, and 2 (1.2%) intolerance. A total of 39/162 (24.1%) patients were treated concomitantly with budesonide and another medication for induction, including loperamide 32/39 (82.1%), bismuth subsalicylate 4/39 (10.2%), and bile acid sequestrant 3/39 (7.7%). In addition, 12/162 (7.4%) patients were treated with a concurrent CYP3A4-inhibitor during induction with budesonide [strong inhibitor 7/12 (58.3%), moderate inhibitor 5/12 (41.7%)].

After induction with budesonide, 96/152 (63.2%) had recurrence after discontinuation; 27/96 (28.1%) required further budesonide induction treatment without maintenance, 56/96 (58.3%) required long-term budesonide maintenance, and 13/96 (13.5%) were treated with other therapies (bile acid sequestrant or bismuth subsalicylate). The median time to recurrence after induction was 98 (7–3,221) days. The initial and lowest effective maintenance dose for those receiving long-term therapy is shown in Table 2. A total of 14/56 (25.0%) patients were treated concomitantly with budesonide maintenance and another medication, including loperamide 12/14 (85.7%), bismuth subsalicylate 1/14 (7.1%), and bile acid sequestrant 1/14 (7.1%). Additionally, 4/56 (7.1%) patients were treated with a concurrent CYP3A4-inhibitor during budesonide maintenance [strong inhibitor 2/4 (50%),

moderate inhibitor 2/4 (50%)]. Of those receiving budesonide maintenance, all responded [55 (98.2%) complete, 1 (1.8%) partial] and none recurred while on maintenance therapy. After discontinuation of maintenance, 26/56 (46.4%) had recurrence, and budesonide was restarted in most [23/26 (88.5%)] for maintenance. The median time to recurrence after discontinuation of the first maintenance was 336 (7–2,885) days. The median duration of the first maintenance treatment was 43 (8–323) weeks and cumulative duration of all maintenance treatments was 62 (16–469) weeks. The median duration of follow-up was 5.6 years (0.3–18.9) and no patient stopped maintenance therapy due to adverse events.

Patients developed the following conditions during budesonide maintenance treatment or within 12 months of discontinuation: osteopenia 6/56 (10.7%), osteoporosis 3/56 (5.4%), diabetes mellitus 1/56 (1.8%), hypertension 0/56 (0%), glaucoma 4/56 (7.1%), cataracts 6/56 (10.7%), and mood changes 6/56 (10.7%) (Table 3). Two (50%) patients on a concurrent CYP3A4-inhibitor during budesonide maintenance treatment developed one of the conditions above. One (1.8%) patient with pre-existing diabetes and 10 (17.9%) with pre-existing hypertension required initiation of a new medication or increased dose of existing medication. Thirty (53.6%) patients received calcium or vitamin D supplementation during maintenance. MC patients not treated with budesonide developed the following conditions within 12 months of diagnosis: osteopenia 6/56 (10.7%), osteoporosis 6/56 (10.7%), diabetes mellitus 0/56 (0%), hypertension 1/56 (1.8%), glaucoma 1/56 (1.8%), and cataracts 7/56 (12.5%). There were no significant differences in individual adverse events between cases and controls [osteopenia (p = 0.47), osteoporosis (p = 0.49), diabetes mellitus (p = 1.0), hypertension (p = 1.0), glaucoma (p = 0.36), cataracts (p = 0.74)] and overall safety outcomes (p = 0.53).

Discussion

In this study, we describe the clinical outcomes and safety profile of budesonide maintenance in MC. While budesonide is the recommended first-line treatment for moderate-severe MC, only 162 (36.0%) were treated with budesonide during the study period, reflecting that patients with mild symptoms were managed with bismuth subsalicylate and antidiarrheals. Furthermore, fewer patients were treated with budesonide during the first half of the study period while it became a more commonly used treatment in the second half of the study period.

Consistent with prior studies, we found a high rate of response and a high rate of recurrence after discontinuation of budesonide.[12–17] In these patients, low-dose budesonide is often used for maintenance therapy. In our cohort, most patients maintained symptomatic response with budesonide 3 mg per day or every other day. Table 4 summarizes previous randomized placebo-controlled trials evaluating both budesonide induction and maintenance treatment for MC, including the clinical outcomes and adverse events.

As reported previously[18–21], long-term budesonide appears to be generally well tolerated; no patients on maintenance therapy discontinued budesonide due to side effects in our cohort. Additionally, the overall incidence of possible budesonide-related adverse effects (metabolic bone disease, hypertension, diabetes mellitus, and ophthalmologic conditions) was relatively

low. We found a similar incidence of adverse events in patients with MC from the REP, matched by age and gender, who were not treated with budesonide. MC occurs frequently in older patients with a female predominance, both known risk factors for metabolic bone disease. It is possible that the incidence of osteopenia/osteoporosis seen in our patients may be in part attributed to these factors, rather than budesonide use alone, although studies have demonstrated the risk of osteoporosis in MC is not increased.[22–25] Similarly, the incidence of ophthalmologic diseases, such as cataracts, seen in our population may also be in part attributed to increasing age.[26–27]

Although budesonide is preferred to other corticosteroids, such as prednisone, due to its high first-pass hepatic metabolism with fewer systemic adverse effects, its metabolism is subject to drug interactions. Medications that inhibit CYP3A4 may have the potential to accentuate the adverse effects of budesonide. About 50% of the patients on a concomitant CP3A4-inhibitor during budesonide maintenance treatment developed a side effect, suggesting this may be an important consideration when selecting maintenance therapy for patients. Although our study is limited by the relatively small sample size, its strengths include the population-based cohort and longitudinal follow-up.

In summary, the long-term use of budesonide in MC appears to be effective and generally well tolerated with limited adverse effects not dissimilar from those with MC not treated with budesonide. Larger, prospective studies are needed to determine the efficacy and safety of long-term budesonide for maintenance in MC.[28]

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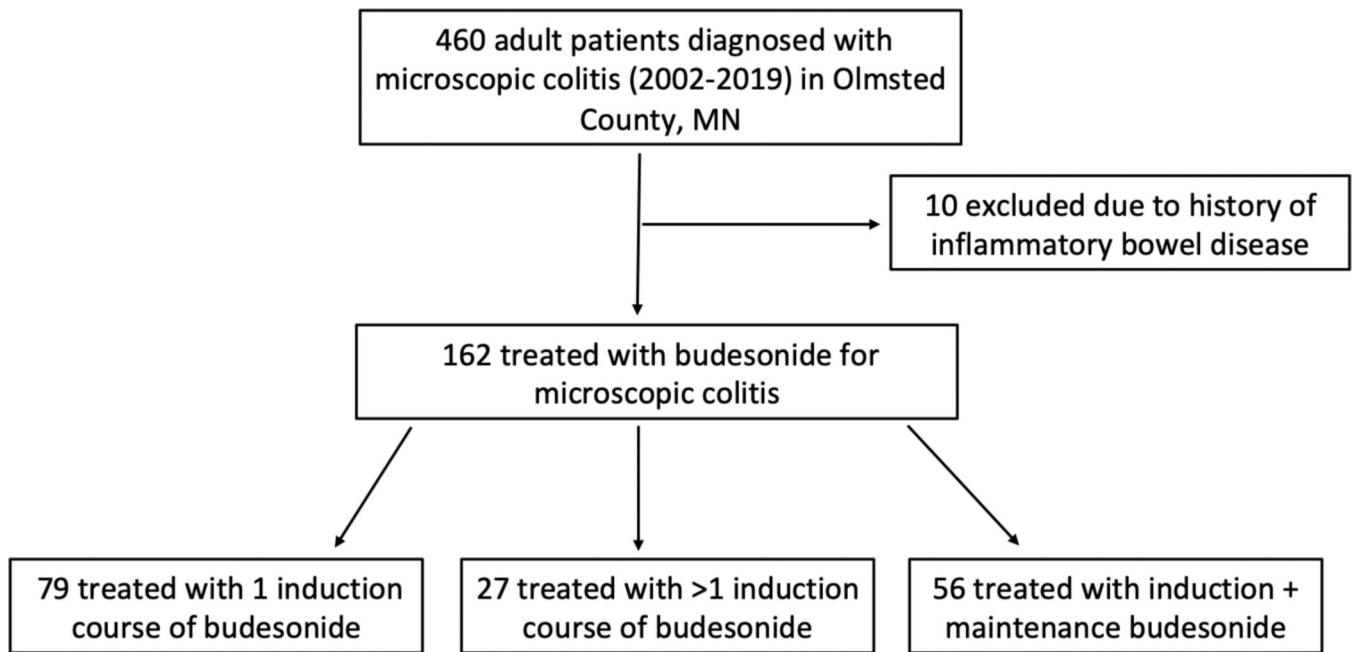
Figure 1.
Study flow diagram.

Table 1.

Baseline characteristics of microscopic colitis patients.

Characteristics		Median (range) or n (%)			
		All patients (n=162)	Lymphocytic colitis (n=78)	Collagenous colitis (n=84)	p-value
Age		67 (23–91)	67 (28–91)	67 (23–88)	0.52
Sex, female		126 (77.8%)	61 (78.2%)	65 (77.4%)	0.89
Race, white		161 (99.4%)	78 (100%)	83 (98.8%)	0.33
Body mass index (kg/m^2)		26.7 (15.8–58.4)	27.5 (15.8–58.4)	26.1 (18.2–48.2)	0.06
Medical Conditions	Hypertension	100 (61.7%)	44 (56.4%)	56 (66.7%)	0.18
	Diabetes mellitus	17 (10.5%)	5 (6.4%)	12 (14.3%)	0.10
	Osteopenia	60 (37.0%)	27 (34.6%)	33 (39.3%)	0.54
	Osteoporosis	25 (15.4%)	9 (11.5%)	16 (19.0%)	0.19
	Glaucoma	14 (8.6%)	7 (9.0%)	7 (8.3%)	0.88
	Cataracts	54 (33.3%)	27 (34.6%)	27 (32.1%)	0.74

*Pre-existing medical conditions prior to budesonide treatment

Table 2.

First maintenance treatment with budesonide.

First maintenance		Median (range) or n (%)		
		All patients (n=56)	Lymphocytic colitis (n=19)	Collagenous colitis (n=37)
Bowel movements, number		5 (3–15)	5 (3–15)	6 (3–15)
Smoking history		39 (69.6%)	10 (52.6%)	29 (78.4%)
Maintenance duration, days		302 (56–2,258)	113 (56–1,387)	379 (84–2,258)
Maintenance initial dose	6 mg daily	43 (76.8%)	12 (63.2%)	31 (83.8%)
	3 mg daily	13 (23.2%)	7 (36.8%)	6 (16.2%)
Maintenance lowest dose	6 mg daily	10 (17.9%)	5 (26.3%)	5 (13.5%)
	3 mg daily	40 (71.4%)	13 (68.4%)	27 (72.9%)
	3 mg every other day	6 (10.7%)	1 (5.3%)	5 (13.5%)
Maintenance outcome	Complete	55 (98.2%)	19 (100%)	36 (97.3%)
	Partial	1 (1.8%)	0 (0%)	1 (2.7%)
	No response	0 (0%)	0 (0%)	0 (0%)
	Intolerance	0 (0%)	0 (0%)	0 (0%)
Recurrence		26 (46.4%)	4 (21.1%)	22 (59.5%)

Table 3.

Safety outcomes within 12 months after completing first maintenance treatment.

First Maintenance		Median ± Range or n (%)		
		All patients (n=56)	Lymphocytic colitis (n=19)	Collagenous colitis (n=37)
Osteopenia*		6 (10.7%)	3 (15.7%)	3 (8.1%)
Osteoporosis*		3 (5.4%)	0 (0%)	3 (8.1%)
Glaucoma*		4 (7.1%)	1 (5.3%)	3 (8.1%)
Cataracts*		6 (10.7%)	2 (10.5%)	4 (10.8%)
Mood changes		6 (10.7%)	2 (10.5%)	4 (10.8%)
Hypertension	New diagnosis	0 (0%)	0 (0%)	0 (0%)
	New or increased dose of current medication	10 (17.9%)	1 (5.3%)	9 (24.3%)
Diabetes mellitus	New diagnosis	1 (1.8%)	0 (0%)	1 (2.7%)
	New or increased dose of current medication	1 (1.8%)	0 (0%)	1 (2.7%)

*
n=39 (69.6%) and n=5 (8.9%) did not have DEXA or ophthalmology exam during or within 12 months after maintenance, respectively

Table 4A.

Randomized control trials of budesonide for induction in microscopic colitis.

Studies	Efficacy	Safety
Miehlke et al. (2002) [12]	86.9% clinical remission in budesonide group vs. 13.6% placebo group (p < 0.001)	7.7% discontinued budesonide due to side effects vs. 4.0% placebo group
Baert et al. (2002) [13]	8/14 patients in budesonide group had clinical remission vs. 3/14 in placebo (p = 0.05)	No serious adverse events reported in either group
Bonderup et al. (2003) [14]	10/10 patients in budesonide group had clinical remission vs. 2/10 in placebo (p < 0.001)	No side effects were reported in either group
Miehlke et al. (2009) [15]	86% clinical remission in budesonide group vs. 48% placebo group (p = 0.10)	10% had side effects in budesonide group vs. 14% in placebo group
Miehlke et al. (2014) [16]	80% clinical remission in budesonide group vs. 37.8% placebo group (p = 0.0006)	The rate of adverse events did not differ between groups
Miehlke et al. (2018) [17]	79% clinical remission in budesonide group vs. 42% placebo group (p = 0.01)	47.4% adverse events in budesonide group vs. 42.1% placebo group

Table 4B.

Randomized control trials of budesonide for maintenance in microscopic colitis.

Studies	Efficacy	Safety
Miehlke et al. (2008) [18]	78% clinical remission in budesonide group vs. 39% placebo group (p = 0.007)	No serious adverse events reported in either group
Bonderup et al. (2009) [19]	76.5% clinical remission in budesonide group vs. 12% placebo group (p <0.001)	Side effects did not differ between groups (1/17 patients in budesonide vs. 1/17 placebo)
Munch et al. (2016) [20]	61.4% clinical remission in budesonide group vs. 16.7% placebo group (p < 0.001)	No serious adverse events reported in either group