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Clinical Evaluation of Budesonide Therapy in Patients with Microscopic Colitis - A Retrospective Cohort Study

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Abstract

Objectives: Budesonide is the first-choice therapy to achieve and maintain clinical remission in microscopic colitis (MC), however the optimal duration of therapy is still unclear. This study aimed to evaluate budesonide therapy in a single-center cohort with long-term follow-up, focusing on relapse rates and steroid dependency.

Methods: All patients with histologically proven MC at the Catharina Hospital between February 2009 and May 2018 were retrieved from the Dutch histopathology database. Patients were categorized into different budesonide regimen groups. The primary outcome was medication free clinical remission related to budesonide therapy. Second, duration and dosage of budesonide therapy and immuno-modulating therapy in refractory MC was evaluated.

Results: In total 89 MC patients were included. Median follow-up was 34.8 months (IQR 17.6-63.0). Fourteen patients (16%) achieved clinical remission either without medication or following non-steroid therapy. Seventy-five patients (84%) were treated with budesonide, of whom 27 (36%) with a single and 17 (19%) with intermittent budesonide courses. Following induction therapy, 69 patients (92% achieved remission. However, during long term follow-up 42 (56%) experienced at least one relapse, indicating the need for maintenance treatment in many cases. Only 27 (36%) of all 75 budesonide treated patients were able to maintain budesonide free clinical remission. Forty-one (54.7%) had chronic/relapsing MC and seven (9.3%) needed immunomodulators.

Conclusions: Budesonide is effective as induction therapy for patients with MC. Many patients need budesonide-maintenance, in contrary to the treatment guidelines. We suggest guiding budesonide therapy by clinical symptoms rather than by a fixed time frame.

Keywords: Microscopic; Immunomodulators; Microscopic Colitis; Budesonide

Introduction

Microscopic colitis (MC) is an inflammatory disease of the colon with three histopathological subtypes: collagenous colitis (CC), lymphocytic colitis (LC), and incomplete microscopic colitis (MCi) [1, 2] Over the past decade, the MC incidence has increased worldwide, however with a varying range of 3.4 to 25 cases per 100,000 person-years [3-5]. The mean incidence is 4.1 CC and 4.9 LC cases per 100,000 person-years [6] . Possibly, growing awareness plays a role in the increased incidence. The three subtypes of MC are not distinguishable by clinical symptoms as all patients have chronic, watery,

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non-bloody diarrhea. Other symptoms include nocturnal stools, abdominal pain, weight loss, fatigue, urgency and incontinence [7]. Since endoscopy may be macroscopically normal, the diagnosis depends on histological findings in colonic biopsies [3]. MC is thought to be a multifactorial disease, predominantly diagnosed in females of advanced age [8]. The current hypothesis is that several luminal and mucosal agents may trigger an uncontrolled immune response in genetically predisposed individuals [6, 9]. This immune-related pathogenesis has been confirmed in a genome-wide study that identified several HLA-polymorphisms associated with MC [10]. A correlation with auto-immune diseases, such as celiac disease has also been demonstrated [7, 11]. More specific risk factors like medication such as non-steroidal anti-inflammatory drugs (NSAIDs), statins and selective serotine re-uptake inhibitors (SSRI, smoking cigarettes and exposure to exogenous estrogens have been identified, but solid evidence-based conclusions cannot be made due to the lack of data [3, 6, 12, 13].

The goal of MC treatment is obtaining and remaining clinical remission by reducing the number of bowel movements and therefore improving quality of life [14]. Histological remission is not a primary treatment goal to date [12]. To obtain clinical remission, budesonide plays a key role in the MC therapy. Budesonide has low systemic bioavailability compared to other corticosteroids due to an extensive first pass mechanism of the small intestine and the liver and is thus generally well tolerated [6, 7].

A meta-analysis of six RCTs showed a relative chance of 2.52 (95% CI 1.45-4.40) of clinical remission when budesonide was compared to no treatment [15]. Moreover 1 of 3 patients will go in remission after a single round of treatment [16]. Specifically for LC this translates to a clinical remission rate of 79-86% after 6-8 weeks versus 42-48% using a placebo [17, 18]. Similar results apply for CC with 80% versus 59.5% after 8 weeks of treatment [19].

The American Gastroenterological Association (AGA) guideline, published in 2016, strongly recommended budesonide 9 mg/day to achieve remission and to consider tapering off towards the lowest possible dose after 8 weeks of treatment [15].

Regardless of the key role in achieving primary remission, 27-61% of patients experience a relapse after budesonide cessation [20-22]. Furthermore, relapse seems to occur independent of the duration of budesonide induction therapy [23]. Nevertheless, quality of evidence was reported as low [24, 25]. Since 2012, the European Microscopic Colitis Group (EMCG) defined several treatment recommendations. This states that in relapse after budesonide withdrawal, this may again be treated with intermitted or low-dose budesonide [26].

Until recently it was unclear how long budesonide should be continued to maintain long-term remission after induction therapy. Guidelines suggested that a short induction course of budesonide therapy would be sufficient to reach and maintain remission [26]. However, only short-term studies with maximum follow-up of 12 months have been published until recently [24, 27]. In 2020, EMCG recommended low dose (3-6 mg) budesonide therapy for CC to maintain remission based on a pooled analysis of three randomized controlled trials (RCT) in CC patients [12]. In total, 68% of the patients maintained in remission with 6 mg of budesonide for 6 months, after induction therapy, versus only 20% in the placebo group [24]. When using 3 mg budesonide for 12 months versus a placebo similar results were found. This was only proven effective in CC and has not yet been examined in LC [12, 25]. In fact, long-term follow-up studies about budesonide in MC are lacking.

Therefor the aim of this retrospective cohort study was to investigate the effect of budesonide therapy in a long-term follow-up cohort of MC patients, and to thereby may support the latest guidelines.

Materials and Methods

Setting & study population

In this single-center retrospective cohort study, all patients were treated for histologically proven MC at the Catharina Hospital Eindhoven, the Netherlands between February 1, 2009 and May 1, 2018 and were identified in the Dutch national registry of histo- and cytopathology (PALGA). [28] Pathology reports and corresponding medical records were reviewed to verify the diagnosis. Patients were included if:

1) ≥ 18 years old
2) having a histological confirmed diagnosis of CC or LC and
3) having at least one episode of clinically active MC based on the Hjortswang criteria (≥ 3 stools per day or ≥ 1 watery stool per day in 1 week) or patient reported stool frequency. [29] Patient characteristics, type of MC, therapy and the number of relapses were collected from patient electronic medical records.

In common clinical practice alternative options to the current EMCG protocol may be used. As different patients may have different responses to a standardized treatment regimen of 9 mg daily of budesonide for 6-8 weeks. Therefore, the primary outcome was budesonide-free clinical remission. Secondary outcomes were treatment duration median cumulative dose, and adverse events related to budesonide. To clarify, the treatment methods used in our hospital and to evaluate their effects on clinical remission and relapse

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rate, patients were divided into four groups according to treatment regimen (see Table 1). Group 3 included all various budesonide therapies. To point out the aim of this study, only data per phenotype will be discussed in the Results section. Comprehensive data will be displayed in Table 5.

Patients were pooled based on the therapy they were using. Most patients started according to the EMCG guidelines. A relapse was defined as clinically active disease according to the treating physician, and/or the Hjortswang criteria [29]. In case a relapse occurred, it was treated with either the lowest possible maintenance budesonide dose (<6 mg/day) or patients were restarted with 9 mg/day, which was tapered off to the lowest possible dose, according to the guidelines [12, 26].

Table 1: Definitions of treatment regimens used in patients with microscopic colitis.

Phenotype	Code	Definition
Quiescent course	1	No treatment / spontaneous remission / withdrawal MC-associated drugs
	2	Other, non-steroidal medication (fibres / chronic loperamide / cholestyramine / mesalamine / sulfasalazine)
Maintenance after therapy	3a	Single budesonide treatment course without relapse
	3b	Budesonide treatment course followed by ≥1 relapse, but no maintenance therapy
Chronic active disease	3c	Budesonide induction- and maintenance therapy (independent from the number of relapses)
	3d	Budesonide treatment followed by or in combination with immune modulating therapy
	4	Immune modulating maintenance therapy

Statistics

Continuous variables were given as a mean with standard deviation (SD) or a median with interquartile range (IQR), depending on normality. Categorical variables were given as numbers and percentages. Differences in continuous variables between treatment groups and outcomes were calculated with variance-analyses, depending on normality. Differences in categorical variables were analyzed with Chi-Square tests or Fisher's exact tests. The statistical package SPSS (IBM SPSS Statistics 25, Armonk, NY) was used to analyze data. The study protocol was approved by the local medical ethical committee**.** No written informed consent was obtained, because the study had a non-interventional, retrospective character with anonymous, non-traceable patient data.

Results

The pathology registry search revealed 108 patients with a possible diagnosis of MC who were treated in the Catharina Hospital Eindhoven between February 1, 2009 and May 1, 2018. Nineteen individuals of these 108 were excluded from the study because of inconclusive pathology reports or not meeting the clinical criteria. Demographic data of the included 89 patients are listed in Table 2. The median age at diagnosis was 68 years (IQR 59 – 76) and patients were predominantly female (75%). Patients were monitored for a median duration of 34.8 months (IQR 4 - 111,5). CC was diagnosed in 55%, LC in 43% and two patients (2%) had MCi. Patients were mostly referred by their general practitioner (75%) and the predominant symptom at first presentation was loose stools (93.3%) with a mean stool frequency of 6.4±3.1 times/day. Other symptoms included nocturnal stools, abdominal pain, weight loss, fecal urgency, and fecal incontinence. Most patients had chronic symptoms (70%) with a median duration of 12.0 weeks before diagnosis (IQR 7.5 – 24.5). The prevalence of several risk factors, including smoking habits and the use of specific drugs (NSAIDs, PPIs and SSRIs) and other diseases linked to MC are described in Table 2.

Eighty-two (92%) patients received any medication during disease course, of whom 75 (91%) used oral budesonide at a certain moment in their disease course. Other prescribed drugs are listed in Table 3. In total, 39 of 82 (48%) patients received maintenance therapy, which could either be budesonide, thiopurines or otherwise.

Twelve patients (14%) with severe or refractory MC needed immune modulating therapy such as thiopurines. Remission rate after induction was 75%, however, 67% reported adverse events, leading to withdrawal in 50% of patients. Eventually, seven refractory MC patients (58%) were on thiopurine maintenance therapy. The other five received budesonide maintenance therapy again. No patient of these two subgroups was able to quit medication (Table 3).

Budesonide Therapy

When focusing in detail on budesonide therapy, 24 (32%) of all 75 patients received 9 mg for 6-8 weeks, in accordance with the EMCG guidelines (Table 4)[12]. Twenty-six (35%) used budesonide for a shorter time or less than 9 mg dose and the remaining twenty-five patients (33%) were treated with a longer induction course.

Ninety-two percent (69/75) of patients achieved clinical remission after all types of budesonide induction courses. When treating 6-8 weeks according to current guidelines, 96% achieved remission, nevertheless 54% relapsed. Whereas twenty-seven patients (36%) only needed one

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Table 2: Patient characteristics of the microscopic colitis cohort.

		N	%
Total study population		89	100
Age of onset (median in years)		68 (IQR 59 – 76)	
Follow-up duration (median in months)		34.8 (IQR 4 – 111.5)	
Gender	Male	23	25.8
	Female	66	74.2
Referred by	General practitioner	67	75.3
	Other	22	24.7
Complaints	Loose stool	83	93.3
	Stool frequency / day?	6.4 (SD 3.1)	
	Nocturnal stools* documented in 36 cases (40%)	27	75.0
	Blood in stool	4	4.5
	Abdominal pain* documented in 86 cases (97%)	30	34.9
	Weight loss* documented in 82 cases (92%)	40	48.8
Duration of complaints before diagnosis* documented in 81 cases (91%)	Median (weeks)	12.0 (IQR 7.5 – 24.5)	
	Acute (≤ 4 weeks)	11	13.6
	Chronic (> 4 weeks)	70	78.7
Endoscopic abnormality	Patchy erythema	16	18
Histopathology	CC	49	55.1
	LC	38	42.7
	MCi	2	2.2
Smoking habits* documented in 80 cases (90%)	Current	26	32.5
	Past	19	23.8
	Never	35	43.8
Medication	PPI	40	44.9
	NSAID	14	15.7
	SSRI	8	9.0
Auto-immune diseases	Celiac disease	4	4.5
	RA	3	3.4
	Type 1 diabetes	2	2.2
	Thyroid disease	7	7.9

* Only known cases were used to calculate percentages.

N = number of patients; CC = collagenous colitis, LC = lymphocytic colitis, MCi = incomplete microscopic colitis, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, SSRI = selective serotonin reuptake inhibitor, RA = rheumatoid arthritis.

Continuous variables were given as mean with SD or as median with IQR (25^{th} and 75^{th} percentiles).

Table 3: Differentiation of MC therapy in all 82 MC patients treated with medication (for either induction, relapse, maintenance or symptomatic).

Medication type	N	Percentage
Budesonide orally	75	91.5
Thiopurine	12	14.6
Psyllium fibers	6	7.3
Loperamide	5	6.1
Mesalazine	4	4.9
Sulfasalazine	3	3.7
Laxatives	3	3.7
Prednisone	2	2.4
Doxycycline	2	2.4
Other	7	8.5

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course of budesonide therapy to achieve and maintain clinical remission, seventeen patients (23%) could not stop the first continuous course of budesonide. Eventually 42/75 patients (56%) relapsed at least once. Six patients (8%) relapsed three times or more. Amongst the different budesonide treatment groups, no significant difference in relapse was found (p = 0.557). Twenty-five patients (33%) could not maintain clinical remission without budesonide and therefore needed maintenance therapy with a median of 3.0 mg/day (IQR 3.0-3.0). Either numerous courses of budesonide or maintenance therapy was necessary in 48 patients (64%) (Table 5).

The median cumulative dose before budesonide interruption was 861.0 mg (IQR 756.0 – 1039.5). Adverse events of budesonide were reported in 15 patients (20%). Twelve patients (16%) with refractory disease or intolerance for budesonide were treated with a thiopurine of whom six (50%) had to stop due to adverse events (fatigue, nausea, constipation, muscle cramps and/or pain, bruising, weight gain, itchy eyes, diplopia and decreased vision). No significant difference was found in remission or relapse between patients treated with 9 mg 6-8 weeks, as suggested by the 2020 EMCG guidelines, and all the other types of courses for remission and relapse (p = 0.389 and p = 0.381).

Overall treatment results

Table 5 shows the main results per budesonide treatment regimen. Fourteen patients (16%) did neither receive any medication (N=7) nor budesonide as first line treatment (N=7)). Seventy five patients (84%) used budesonide at some point of their MC disease course. Patients with a chronic active disease may have also received immunosuppressive therapy due to lack of effectivity of budesonide or adverse side effects. There were no significant difference in duration of symptoms (8-12 weeks) and daily stool frequency (6.0-7.5) prior to treatment for the remission after treatment and chronic active disease groups.

In total, 82 patients (92%) were in remission either without medication or after any form of induction therapy. Sixty-nine (92%) of all 75 patients that were treated with budesonide induction therapy achieved remission, however only thirty-one (41%) of these patients maintained in remission. In total at least one relapse occurred in 42 budesonide patients (56%). CC patients showed a worse outcome compared to LC with more frequent courses of budesonide, maintenance therapy or immune modulating therapy. Other parameters as stool frequency and duration of complaints showed no significant differences between all the groups.

Table 4: Outcomes of budesonide induction therapy.

Budesonide therapy	All MC (%)	CC	LC	MCi	Cumulative dose (mg)	Remission	Relapse	Adverse events
< 6 weeks 9 mg	24 (32.0%)	15 (62.5%)	8 (33.3%)	1 (4.2%)	504.0 (IQR 504.0-556.5)	22 (91.7%)	10 (41.7%)	4 (16.7%)
6-8 weeks 9 mg (EMCG guideline 2020)	24 (32.0%)	9 (37.5%)	15 (62.5%)	0 (0.0%)	861.0 (IQR 756.0-1039.5)	23 (95.8%)	13 (54.2%)	3 (12.5%)
> 8 weeks 9 mg with stop	17 (22.7%)	13 (76.5%)	3 (17.6%)	1 (5.9%)	1155 (IQR 1008.0-1559.3)	15 (88.2%)	11 (64.7%)	4* (25.0%)
> 8 weeks 9 mg without stop	6 (8.0%)	2 (33.3%)	4 (66.7%)	0 (0.0%)	1680.0 (IQR 1179.0-1879.5)	5 (83.3%)	4 (66.7%)	2 (33.3%)
9 mg – duration unknown	2 (2.7%)	1 (50.0%)	1 (50.0%)	0 (0%)	Unknown	2 (100%)	2 (100%)	1 (50.0%)
Other than 9 mg	2 (2.7%)	2 (100.0%)	0 (0.0%)	0 (0%)	1407.0 (IQR 882.0-1932.0)	2 (100%)	1 (50.0%)	1 (50.0%)
Total number (%)	75 (100%)	42 (56.0%)	31 (41.3%)	2 (2.7%)	-	69 (92.0%)	41 (54.7%)	15 (20.0%)

*CC = collagenous colitis, LC = lymphocytic colitis and MCi = incomplete microscopic colitis. * 1 unknown case excluded. Cumulative dose = for the entire follow-up*

Table 5: Outcomes of different treatment regimens in MC.

Group	Medication	N	MC type			Remission after induction therapy	Relapse	Median relapse free period in months (IQR)	Any maintenance therapy	Median follow-up in months (IQR)	Adverse events	Mean age (SD)	Median duration of complaints in weeks (IQR)	Median stool frequency at presentation (IQR)
			CC	LC	MCi									
1	No medication	7 (7.9%)	3 (42.9%)	4 (57.1%)	0	-	0	44.0 (27.5-71.0)	-	44.8 (27.3-71.0)	-	74.0 (13.2)	12.0 (3.0-16.0)	3.0 (2.0-3.0)
2	Medication except budesonide	7 (7.9%)	3 (42.9%)	4 (57.1%)	0	7 (100%)	2 (28.6%)	31.8 (22.5-38.0)	1 (14.3%)	32.5 (31.5-42.0)	-	73.3 (S7.6)	11.0 (3.3-28.0)	8.0 (3.0-10.0)

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3a	Budesonide single course	27 (30.3%)	14 (51.9%)	13 (48.1%)	0	27 (100%)	0	20.3 (8.0-33.5)	1 (3.7%)	22.3 (9.3-44.8)	3 (11.1%)	67.8 (14.5)	12.0 (6.5-21.0)	6.0 (5.0-8.0)
3b	Multiple budesonide courses	17 (19.1%)	8 (47.1%)	9 (52.9%)	0	13 (76.5%)	17 (100%)	4.5 (3.3-7.3)	2 (11.8%)	56.5 (34.8-77.1)	4 (25%)	58.4 (17.0)	12.0 (8.0-27.5)	6.0 (3.8-8.0)
3c	Budesonide maintenance	20 (22.5%)	13 (65.0%)	6 (30.0%)	1 (5.0%)	19 (95%)	14 (70.0%)	5.8 (2.6-12.2)	20 (100.0%)	26.3 (12.3-68.4)	4 (20%)	66.8 (9.3)	12.0 (8.0-25.5)	7.5 (5.0-10.0)
3d	Budesonide and temporary immune therapy	4 (4.5%)	4 (100.0%)	0	0	3 (75%)	4 (100%)	4.5 (2.0-4.5)	4 (100.0%)	89.3 (65.6-10.8)	3 (75%)	62.3 (6.9)	91.0 (19.0-032.3)	6.0 (5.3-10.5)
4	Maintenance immunotherapy	7 (7.9%)	4 (57.1%)	2 (28.6%)	1 (14.3%)	6 (85.7%)	7 (100%)	4 (2.0-8.0)	7 (100.0%)	39.3 (30.3-59.0)	1 (14.3%)	67.9 (9.4)	8.0 (6.0-20.0)	6.0 (2.8-9.8)
	Total	89 (100%)	49 (55.1%)	38 (42.7%)	2 (2.2%)	75 (91.5%)	44 (49.4%)	9.4 (4.0-31.3)	35 (39.3%)	34.8 (17.6-63.0)	16 (20.8%)	66.4 (13.4)	12.0 (7.5 – 24.5)	6.0 (4.0-8.0)

Discussion

This study aimed to evaluated budesonide therapy in a single center MC cohort with a long-term follow-up of 34.8 months.

Induction of remission

Seventy-five (84.3%) of 89 included patients were treated with budesonide. Following induction therapy, remission was achieved in 92% when taking all budesonide strategies together. When treated with a 6-8 week budesonide induction course according to the 2020 guidelines even 96% reached remission. This indicates that our results of budesonide induction therapy are in accordance with the current guidelines. The percentage is higher than the pooled response rate of 81% in CC and 84% in LC mentioned in both European guidelines from 2012 and 2020, based on Cochrane meta-analyses and a recent meta-analysis by Tome et al. [12, 24-26, 30]. A possible reason for our higher response rate could be the early start with budesonide at our hospital compared to previous studies, due to diagnostic delay in other studies [31-33]. However, the first continuous budesonide course could not be ceased in 17 out of 75 patients (23%). This result is in accordance with previous reports showing either relapsing symptoms or need for continuous budesonide of 6mg/d of more in 17-20% of patients [27, 34, 35].

Sustained remission

Our study with a median follow-up of 34.8 months (IQR 17.6 – 63.0) found sustained remission in 45 (49%) of all 89 MC patients with a median follow-up of 34.8 months (IQR 17.6-63.0) Only 27 (36%) of all 75 budesonide treated patients were able to maintain clinical remission after a single budesonide induction course: 41 (55%) had chronic/relapsing MC and seven (9.3%) needed immunomodulators. Notably, six patients (8.0%) relapsed frequently and were on and off medication multiple times. Therefore, budesonide-free remission is questionable in these patients.

A Cochrane meta-analysis described maintained remission after budesonide in 68% of CC patients, but follow-up duration was only 6 or 12 months in the included trials [24]. In LC this has not been fully examined [12, 36]. Although one study did point out that CC patients need maintenance therapy more frequently compared to LC patients [37]. Yet another LC study (2-year median follow-up) showed 46% clinical remission [38]. A review and meta-analysis of 10 RCTs from Sebastian et al. also examined the maintenance of clinical remission after induction with budesonide, comparing budesonide with placebo maintenance therapy [39]. Results were equal to the earlier meta-analysis: budesonide treated patients also displayed a sustained response in 68% versus 21% in the placebo group (pooled ORs 8.35 (95% CI: 4.14-16.85)) [39]. In addition, relapse rates 12 months after cessation of maintenance budesonide were more than 50%, similar to our findings. This review stated that 82% relapsed even after prolonged budesonide treatment, indicating that a longer duration of therapy does not reduce relapse risk of MC [39]. The median budesonide free remission between relapses was 93 days. In our study this interval was 154 days, but Hajdar et al. even described a period of 437 days [34]. The only published prospective study yet, showed that only 40% of patients achieved sustained remission after budesonide induction in 318 European patients with a shorter, one year follow-up. Fourty-nine percent had chronic active and/or relapsing disease course [40].

Fifteen out of 75 (20%) budesonide treated patients in our study reported adverse events, leading to cessation of therapy in one patient (1.3%). Shaji et al. described no significant difference in adverse events related to budesonide versus placebo therapy. Nevertheless budesonide withdrawal was 15% [39].

No clinical predictors associated with efficacy of budesonide therapy could be found in our study. Previously, stool frequency at time of diagnosis was a factor in one

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study [20]. On the other hand, a recent prospective study showed also none [40]. Thus, severity of symptoms at time of diagnosis seem unusable clinical predictors for efficacy of budesonide therapy of MC.

This study has several strengths. Data was collected from a real-world MC cohort. All patients were included based on pathology results, reducing selection bias. Patients had well registered clinical characteristics and a long follow-up. The study investigated more aspects of budesonide therapy than previous studies, for example cumulative dose. The population size of 89 seems a disadvantage, nevertheless it is larger than previous studies about this relatively rare disease, with only 39-84 patients [24, 25]. Weak points of the study are the retrospective, single center character. The study has a lack of histological control of disease activity, thus the overlap of MC related complaints and irritable bowel symptoms may not be sufficiently examined.

In fact, there is a strong need for large prospective studies on budesonide therapy in MC, to redefine therapeutic criteria, including duration and dosage of maintenance treatment in MC patients among others.

In conclusion, our study shows that many patients need continuous or repetitive budesonide courses to keep MC in remission. When following previous guidelines, 55% of MC patients are not sufficiently treated and need for any form of budesonide maintenance therapy. Based on our cohort study, we suggest that budesonide treatment should be symptom guided, rather than being limited to a predefined duration, as may also be supported by the latest guidelines, published in the meantime. Maintenance budesonide seems the lowest possible dose is effective in patients with persisting symptoms or frequent relapses, as supported by the latest, recently published guidelines [12].

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