Microscopic colitis: An approach to treatment

Nilesh Chande MD FRCPC

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Microscopic colitis – including collagenous colitis and lymphocytic colitis – causes chronic watery diarrhea, usually in middle-aged or elderly patients. There is an association with celiac disease and certain medications. Medical treatment includes various antidiarrheal agents, mesalamine, corticosteroids and immunosuppressant drugs. Rarely, patients require surgery for refractory disease. An evidence-based and practical approach to treatment should optimize the treatment response while minimizing potential adverse events.

Key Words: *Collagenous colitis; Lymphocytic colitis; Microscopic colitis; Treatment*

La colite microscopique : Une approche du traitement

La colite microscopique, incluant la colite collagène et la colite lymphocytaire, provoque une diarrhée aqueuse chronique, généralement chez les patients d'âge mûr ou âgés. Il existe un lien entre la maladie cœliaque et certains médicaments. Le traitement médical inclut divers antidiarrhéiques, la mésalamine, les corticoïdes et les immunosuppresseurs. Dans de rares cas, les patients doivent subir une opération en raison d'une maladie réfractaire. Une approche thérapeutique probante et pratique devrait optimiser la réponse au traitement tout en réduisant au minimum le potentiel d'effets indésirables.

Collagenous colitis and lymphocytic colitis, the two subtypes of microscopic colitis, typically cause diarrhea in middle-aged or older individuals. They share many epidemiological and clinical features, but are distinguished by their histological features. Collagenous colitis is defined by a thickened subepithelial collagen band (thicker than 10 µm), with minimal lymphocytic infiltration. A diagnosis of lymphocytic colitis requires an increased number of intraepithelial lymphocytes (more than 20 lymphocytes per 100 epithelial cells), without a significantly thickened collagen band.

Various therapies have been reported to be effective for treating patients with microscopic colitis, but most randomized, controlled trials have included patients with collagenous colitis only. However, in practice, it seems that treatments for collagenous colitis can be used for lymphocytic colitis as well, with similar benefit. Because microscopic colitis generally is a benign disorder that does not lead to serious consequences such as weight loss or malnutrition, an approach to treatment must consider the severity of the symptoms, particularly when using therapies with potential toxicities. The present review aims to provide a logical approach to treating patients with microscopic colitis, summarizing key evidence for therapy and placing various treatment options into a rational, clinical context.

MEDICATION REVIEW

Although the etiology of microscopic colitis is not clear in most cases, certain medications have been associated with the onset of symptoms. Those most strongly implicated include acarbose, acetylsalicylic acid, Cyclo 3 Fort (Pierre Fabre Medicament, France), lansoprazole, nonsteroidal anti-inflammatory drugs, ranitidine, sertraline and ticlopidine (1). A careful review of a patient's medication history is the first step in managing a patient with microscopic colitis, because stopping treatment with an offending drug may lead to resolution of the symptoms.

RULE OUT CELIAC DISEASE

Celiac disease is a common comorbidity in patients with microscopic colitis, occurring in 15% to 20% of patients (2,3). Patients with microscopic colitis should be screened for celiac disease using serology. A small bowel biopsy is required to confirm the diagnosis. Those patients determined to have celiac disease should be treated with a gluten-free diet. Because there is a considerable overlap of symptoms between celiac disease and microscopic colitis, a gluten-free diet often leads to improvement in diarrhea and other symptoms shared by the two disorders.

MEDICAL THERAPY

Initial and subsequent medical therapies should take into account the severity of the patient's symptoms, the response to previous treatments and the potential toxicity of the prescribed medication. Many patients can be managed with intermittent courses of therapy when their disease is most active; relatively few patients require long-term continuous medical treatment (Table 1).

Antidiarrheals

Antidiarrheal therapy with loperamide or similar medications is usually the first-line medical therapy for patients with microscopic colitis. Many patients will have treated themselves with these types of therapies before presentation to their physician. However, the doses used by self-treating patients may be suboptimal, and high-dose antidiarrheal therapy should not be excluded as a therapeutic manoeuvre when initially managing patients with microscopic colitis. Symptomatic benefit may be

Division of Gastroenterology, The University of Western Ontario, London, Ontario
Correspondence: Dr Nilesh Chande, Mailbox 55, London Health Sciences Centre – South Street Hospital, 375 South Street, London, Ontario N6A 4G5. Telephone 519-667-6582, fax 519-667-6820, e-mail nchande2@uwo.ca
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TABLE 1
Medical therapies for patients with microscopic colitis

Medication	Suggested dosing	Notes	Selected references
Loperamide (or other antidiarrheals)	2 mg po, when necessary (up to eight tablets daily)	Can be used intermittently or regularly. Also effective for breakthrough symptoms when on other treatments	4,5
Bismuth subsalicylate	3 × 262 mg tablets po tid × eight weeks	Possible bismuth neurotoxicity with long-term use. If regular use required, should be taken in an eight weeks on, eight weeks off regimen	6,7,8
Mesalamine	800 mg po tid × six months or longer	Likely effective for inducing and maintaining response if used continuously. Addition of cholestyramine may have additional benefit for collagenous colitis	9
Cholestyramine	4 g po od × six months or longer	Can be used alone or with mesalamine to induce and maintain response	9-11
Budesonide	9 mg po od (or in a tapering course) × six to eight weeks to induce response. 6 mg po od × six months or more to maintain response	Patients that relapse after induction dosing should be considered for maintenance therapy	12-14,17-19
Prednisone	50 mg po od × two weeks, then tapered	Optimal duration of therapy not clear. Should be used for cases of budesonide failure	20
Azathioprine/ 6-mercaptopurine	Azathioprine 2 mg/kg/day to 2.5 mg/kg/day, or 6-mercaptopurine 1 mg/kg/day to 1.5 mg/kg/day, indefinitely	Should be used only for severe steroid-dependent or refractory disease	21,22
Methotrexate	10 mg to 25 mg po weekly, indefinitely	Should be used only for severe steroid-dependent or refractory disease	24

od Once per day; po By mouth; tid Three times per day

seen in a substantial portion of patients when antidiarrheals are used alone, or these therapies can be used in conjunction with others when treating more refractory cases (4,5).

Bismuth subsalicylate

Bismuth subsalicylate is an over-the-counter agent used for various gastrointestinal complaints. It has been studied for the treatment of microscopic colitis, and been found to improve both clinical and histological activity of the disease over the short term, without significant adverse events (6,7). The long-term benefits of this medication are unproven, but it likely can be used effectively to treat patients with relapsing disease. There is a theoretical potential for bismuth toxicity with continuous use, so a regimen of intermittent use is preferred (8).

Mesalamine

Mesalamine, commonly used to treat inflammatory bowel disease, has also been studied for the treatment of microscopic colitis. An open-label, randomized trial (9) demonstrated high clinical and histological responses to mesalamine treatment, with a maintained response over six months and minimal adverse events. The addition of cholestyramine may have some further benefit for patients with collagenous colitis (9). Mesalamine should be considered early in the treatment algorithm, and can likely be used for both induction and maintenance of response for patients with microscopic colitis.

Cholestyramine

Bile acid malabsorption may contribute to the diarrhea seen in some patients with microscopic colitis. Cholestyramine may be effective as monotherapy or when used in conjunction with mesalamine for patients with microscopic colitis (9-11).

Budesonide

Budesonide, a steroid with extensive first-pass metabolism, has the strongest evidence from clinical trials for treating patients with microscopic colitis. Three randomized, placebo-controlled trials (12-14) in patients with collagenous colitis demonstrated that this medication is effective for treating active disease over six to eight weeks, with a pooled response rate of 81% in a meta-analysis (15) (compared with 17% with placebo), a pooled OR of 12.32 and a number needed to treat of two patients. Budesonide was well tolerated, and also improved histology and quality of life (12-16). It was also shown to be effective for maintaining a clinical response in two trials (17,18) of patients with collagenous colitis over a six-month period, with a pooled response rate of 83% (compared with 28% with placebo), a pooled OR with budesonide therapy of 8.40, and a number needed to treat of two patients. A maintained histological response to budesonide was also found (17,18).

A single randomized, placebo-controlled trial (19) of budesonide in patients with active lymphocytic colitis was also positive, with a response rate to budesonide of 86% (and 40% with placebo), and a number needed to treat of three patients. Budesonide has not been studied for maintaining response in patients with lymphocytic colitis, but it probably can be effectively used for this purpose.

Despite the best evidence for efficacy, budesonide should not necessarily be the first-line therapy for all patients with microscopic colitis. It is a corticosteroid; therefore, there is a potential for significant adverse events. Cost and drug coverage issues may also be a limiting factor for some patients. As a result, budesonide is often reserved for patients with severe symptoms or those who fail more benign treatments.

Prednisone

Prednisone has been studied in one small, randomized, placebo-controlled trial (as the active form, prednisolone) (20). This study demonstrated a trend toward benefit with prednisolone. However, the trial was small (it enrolled 11 patients with collagenous colitis and one patient with lymphocytic colitis) and lacked the power to detect a significant difference. Adverse events with prednisone are common;

therefore, it should be used only for patients with disease refractory to budesonide therapy.

Immunosuppressive therapy

Patients who fail to respond to systemic steroids, or relapse when tapering or discontinuing them are candidates for immunosuppressive therapy. Azathioprine or 6-mercaptopurine, and methotrexate are probably the most appropriate choices. However, there are also reports of cyclosporine use (21-25). Dosages should be similar to those used for inflammatory bowel disease, although an oral route rather than a parenteral route for methotrexate is probably sufficient.

SURGICAL THERAPY

Surgical intervention is rarely required for patients with microscopic colitis, and should be reserved for those who fail all medical therapies. Most patients can be managed with a diverting ileostomy without removing the colon. Fecal stream diversion will often lead to histological improvement in the colon. Re-establishing the fecal stream will lead to recurrence of the microscopic colitis, and is not recommended. A proctocolectomy with ileal J-pouch anal anastomosis can be used for selected patients who do not want a permanent ostomy (26-30).

CONCLUSIONS

Collagenous colitis and lymphocytic colitis should be considered as diagnostic possibilities in patients presenting with watery diarrhea, and are diagnosed by a colonoscopy or sigmoidoscopy with biopsies. A positive diagnosis should lead to a review of current and previous medication use, as well as a screening test for celiac disease. The choice of initial medical therapy will depend on symptom severity. Budesonide has the best evidence for efficacy. However, more benign and inexpensive treatments, including antidiarrheals, bismuth subsalicylate, mesalamine and cholestyramine, may suffice. Most patients can manage with intermittent therapy when their symptoms are most severe. Refractory cases will require corticosteroid or immunosuppressive treatments, or even surgical intervention. A logical and stepwise approach to managing patients with microscopic colitis will lead to optimal patient outcomes.

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