BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Overview of microscopic colitis

Omer F Ahmad[1]

Ayesha Akbar[2,3]

Author details can be found at the end of this article

Correspondence to:
Ayesha Akbar; aakbar@nhs.net

Abstract

Microscopic colitis encompasses both collagenous and lymphocytic colitis and is a relatively common condition with rising incidence. Diagnosis is by colonoscopy (which is usually normal but may show some mild changes) and biopsies which reveal characteristic histological findings. Symptoms include non-bloody diarrhoea with urgency which may be associated with faecal incontinence and abdominal pain. Microscopic colitis is associated with a reduced health-related quality of life, and treatment is aimed at symptom control. Medications linked with the development of microscopic colitis, including proton pump inhibitors, non-steroidal anti-inflammatory drugs and selective serotonin-reuptake inhibitors, should be discontinued. If symptoms persist, budesonide is a licensed treatment for microscopic colitis which has been shown to be effective in clinical trials and real-world practice.

Key words: Budesonide; Collagenous colitis; Lymphocytic colitis; Microscopic colitis; Proton pump inhibitors

Submitted: 30 January 2020; accepted following double-blind peer review: 8 June 2020

Introduction

Microscopic colitis is a relatively new condition, first recognised in 1976 as a chronic inflammatory bowel disease which is a major cause of persistent non-bloody watery diarrhoea, particularly in elderly women (Lindstrom, 1976). The incidence and prevalence of this condition has been rising (Tong et al, 2015), highlighting the importance in clinical practice of recognising and diagnosing it. The term microscopic colitis embraces both collagenous and lymphocytic colitis (Lazenby et al, 1989). It is so named as colonoscopy is often macroscopically normal, and it is necessary to take biopsies to identify the histological changes seen. In 1989, Lazenby et al looked at histological specimens from five different groups in a blinded manner: lymphocytic colitis (n=16), collagenous colitis (n=17), idiopathic inflammatory bowel disease (n=16), acute colitis (n=16), and histologically normal colon (n=12). They concluded that there were very close similarities in the biopsies from lymphocytic colitis and collagenous colitis; the most distinctive feature of lymphocytic colitis was increased intraepithelial lymphocytes, but sub-epithelial collagen thickening was seen only in collagenous colitis, making it a distinct entity. The histological changes seen in microscopic colitis were clearly distinguishable from the changes seen in the idiopathic inflammatory bowel disease, acute colitis and normal colon groups. Treatment of collagenous colitis and lymphocytic colitis is similar.

Although the symptoms can significantly impact on quality of life, the prognosis is good – there is no increased risk of colon cancer as is seen with idiopathic inflammatory bowel disease. However, an increased incidence of bile salt diarrhoea and coeliac disease is associated with microscopic colitis. Correct diagnosis is important for appropriate management and to differentiate from irritable bowel syndrome. Further research would be beneficial in this field, in particular looking at the pathogenesis.

Epidemiology

The incidence is similar to that of classic inflammatory bowel disease (ulcerative colitis and Crohn's disease). Tong et al (2015) carried out a review looking across 25 studies and concluded that the pooled incidence rate of collagenous colitis was 4.14 per 100 000 person-years and 4.85 for lymphocytic colitis, with an increased incidence with age. The female-to-male incidence rate ratios were 3.05 (95% confidence interval 2.92–3.19) for collagenous colitis and 1.92 (95% confidence interval 1.53–2.31) for lymphocytic colitis;

How to cite this article:
Ahmad OF, Akbar A. Overview of microscopic colitis. Br J Hosp Med. 2020. https://doi.org/10.12968/hmed.2020.0034

the median age at diagnosis for collagenous colitis was 64.9 years, similar to lymphocytic colitis (median 62.2 years). They found an increased risk of microscopic colitis associated with the use of proton pump inhibitors and selective serotonin-reuptake inhibitors (odds ratio 2.68, 95% confidence interval 1.73–4.17 and odds ratio 2.41, 95% confidence interval 1.64–3.53 respectively).

Risk factors

Several risk factors have been associated with microscopic colitis. These include an association with autoimmune disorders (coeliac disease, thyroid disease, rheumatoid arthritis, type 1 diabetes or psoriasis), smoking and various medications. Fernández-Bañares et al (2013) found the strongest associations for collagenous colitis with a history of polyarthritis (odds ratio, 20.8), and consumption of lansoprazole (odds ratio odds ratio 6.4); and for lymphocytic colitis the greatest association was with current smoking (odds ratio 3.8), associated autoimmune diseases (odds ratio 8), sertraline (odds ratio 17.5), omeprazole (odds ratio 2.7) and low-dose aspirin (odds ratio 4.7). A retrospective study found autoimmune disorders were present in 40% of patients with lymphocytic colitis (Olesen et al, 2004).

Symptoms and pathogenesis

The typical presentation of microscopic colitis is with chronic non-bloody watery diarrhoea. Bohr et al (1996) conducted a retrospective study of 163 patients with collagenous colitis and found all had watery diarrhoea (nocturnal in 27%), with a chronic intermittent course in 85%. Other symptoms included abdominal pain (41%), and weight loss (42%). Olesen et al (2004) similarly looked at a cohort of 199 patients with lymphocytic colitis and found that the commonest presenting symptoms were diarrhoea (96%), abdominal pain (47%), and weight loss (41%). The course was chronic intermittent in 30% of patients, chronic continuous in 7%, and 63% presented with only a single episode. Faecal incontinence, urgency, nausea, bloating and fatigue may also be seen. Studies also indicate a reduced health-related quality of life with microscopic colitis (Nyhlin et al, 2014).

The cause of microscopic colitis is still not clear, and likely to be multifactorial, resulting in a mucosal immune response to luminal triggers in predisposed individuals. There is a common association of bile acid malabsorption with microscopic colitis (up to 44% with patients who have collagenous colitis, and 60% of patients who have lymphocytic colitis) but again it is not clear if this is causal or not (Fernández-Bañares et al, 2001; Münch et al, 2012a).

Diagnosis

Microscopic colitis should be considered in those presenting with non-bloody diarrhoea. After taking a detailed history, including concomitant medications, and examination, routine blood tests should be performed to look for potential causes (full blood count, renal function, coeliac serology, haematinics, thyroid function tests, C-reactive protein). Stool cultures may be appropriate to exclude infection if there is acute onset. Other causes of diarrhoea including lactose malabsorption, coeliac disease and bile acid malabsorption should be excluded, as recommended by the European Microscopic Colitis Group (Münch et al, 2012a).

Faecal calprotectin levels may be raised in patients with microscopic colitis, although not consistently, and may also be elevated when a patient is asymptomatic, so are not useful for monitoring. Various non-invasive biomarkers, including calprotectin, myeloperoxidase, lactoferrin, eosinophil protein X, eosinophil cationic protein, and tryptase, have been investigated but none have been found to be reliable for microscopic colitis (Pisani et al, 2017). Faecal calprotectin measurement does not differentiate between different causes of inflammation, so is not appropriate as a diagnostic tool – patients over the age of 50 years with persistent symptoms should undergo biopsy to allow accurate diagnosis. Faecal calprotectin measurement can lead to patients being misdiagnosed with irritable bowel syndrome which, in the past, has led to underdiagnosis and therefore inappropriate management of those with microscopic colitis.

The most reliable investigation remains colonoscopy, with biopsies taken from each segment of the colon to look for characteristic histological findings (Langner et al, 2015). Thijs et al (2005) found that changes of microscopic colitis were only found in the right colon in 23% of patients, so flexible sigmoidoscopy alone with biopsies may not be adequate to exclude microscopic colitis, and full colonic examination is also recommended to rule out other pathology. In the majority of cases of microscopic colitis, colonoscopy will be macroscopically normal although in a minority various endoscopic findings have been reported including alteration of the vascular mucosal pattern, mucosal nodularity, mucosal erythema or oedema, linear colonic mucosal defects (lacerations, tears or fractures), and mucosal scarring or cat scratch colon (Koulaouzidis and Saeed, 2011; Koulaouzidis et al, 2017). However, none of these findings is pathognomonic of microscopic colitis (Koulaouzidis et al, 2017).

In patients with microscopic colitis, chronic inflammation is seen in the lamina propria. In those with lymphocytic colitis the main histological finding is an increase in surface intraepithelial lymphocytes (T-lymphocytes) of >20 intraepithelial lymphocytes per 100 epithelial cells (Münch et al, 2012a). In borderline cases CD3 staining may be helpful to determine the precise number of intraepithelial lymphocytes (Liszka et al, 2006; Münch et al, 2012a).

In patients with collagenous colitis, the major histological finding is that of a thick subepithelial fibrous band (>10 µm) immediately underneath the surface epithelium. Mucosal inflammation (mild to moderately increased numbers of lymphocytes, plasma cells, mast cells, eosinophils and neutrophils) is also a typical finding in collagenous colitis. The epithelium itself may have changes including vacuolisation and desquamation as well as increased intraepithelial lymphocytes (but not as many as seen in lymphocytic colitis) (Münch et al, 2012a).

Management

Treatment strategies for microscopic colitis should aim to induce clinical remission from symptoms and improve quality of life. In cases of relapse, pharmacological treatment can be used to maintain remission. Treatment is guided by symptomatic response, with no current reliable biomarkers available to monitor disease activity. While assessing histological healing is important in predicting disease course in classical inflammatory bowel disease, there is a paucity of evidence to support a similar approach in microscopic colitis, hence repeat biopsies are not routinely recommended.

Avoidance of potential exacerbating factors

Initial management should involve the avoidance of exacerbating factors, such as smoking, and drugs associated with microscopic colitis. Common medications that should be avoided include non-steroidal anti-inflammatory drugs, proton pump inhibitors and selective serotonin-reuptake inhibitors. If medications cannot be discontinued then an intra-class switch to a drug with a lower associated risk can be considered, for example, omeprazole rather than lansoprazole. A more extensive list of potential drugs associated with microscopic colitis can be found in the review by Beaugerie and Pardi (2005), but it is important to note that a large proportion of these implicated medications are also associated with chronic diarrhoea as an adverse effect. Furthermore, evidence suggesting a clear cause–effect relationship is lacking in most cases, which ideally requires more detailed evaluation of temporal symptoms and histological activity following re-introduction of potential offending drugs.

Medical treatment

Budesonide

A number of pharmacological options have been proposed for the treatment of microscopic colitis. Budesonide is widely accepted as first-line therapy, as it is the only drug with demonstrable efficacy in randomised controlled trials and meta-analyses (Miehlke et al, 2019; Sebastian et al, 2019). This is reflected in international guidelines and statements produced by the American Gastroenterological Association (Nguyen et al, 2016) and the European Microscopic Colitis Group (Münch et al, 2012a).

Seven randomised controlled trials have evaluated budesonide for clinical induction of microscopic colitis, including four for use in collagenous colitis (Baert et al, 2002; Miehlke et al, 2002, 2014; Bonderup et al, 2003) and three for use in lymphocytic colitis (Miehlke et al, 2009, 2018; Pardi et al, 2009). A systematic review and meta-analysis calculated a pooled odds ratio of 7.34 (95% confidence interval 4.08–13.19) for a response to budesonide at induction in microscopic colitis after 6–8 weeks of treatment (Sebastian et al, 2019). The response was comparable for both collagenous colitis and lymphocytic colitis subtypes.

Relapse following cessation of budesonide frequently occurs in patients with microscopic colitis. Three randomised controlled trials have been conducted for use of budesonide as maintenance therapy in patients with collagenous colitis subtype only (Miehlke et al, 2008; Bonderup et al, 2009; Münch et al, 2016). After remission was achieved, budesonide 4.5–6 mg per day was taken for 6–12 months, resulting in a pooled odds ratio of 8.35 (95% confidence interval 4.14–16.85) for a response to budesonide (Sebastian et al, 2019). While there are no randomised controlled trial data on budesonide maintenance therapy in patients with the lymphocytic colitis subtype at this time, it is reasonable in clinical practice to assume that a similar effect would be seen as that for collagenous colitis.

Budesonide undergoes extensive first-pass metabolism and therefore has very low systemic bioavailability. Meta-analyses have found similar adverse events rates to placebo, with no significant safety concerns. Patients are therefore not routinely monitored for adverse effects seen with traditional glucocorticoids such as prednisolone, although clinicians should be mindful of these occurring rarely with long-term use (Tripathi and Dunzendorfer, 2017).

Other therapies

Strong evidence is lacking for therapies other than budesonide in microscopic colitis, although some are frequently used in clinical practice. Loperamide has not been formally studied in a trial setting, but may provide some symptomatic benefit from diarrhoea, although this is unlikely to address the underlying inflammatory component of microscopic colitis. Retrospective studies suggested a possible response to mesalazine, but subsequent randomised controlled trials demonstrated no benefit over placebo (Miehlke et al, 2014, 2018). Prednisolone is considered to be less effective than budesonide according to a meta-analysis, although it has only been investigated in one small randomised controlled trial (12 patients). Bismuth subsalicylate has been reported as being more effective than placebo in a small randomised controlled trial (14 patients), but this trial has not been fully published (Fine et al, 1999). Cholestyramine demonstrated some benefit in patients with collagenous colitis in a randomised controlled trial when combined with mesalazine, and compared with mesalazine alone, but this was an open-label study with no placebo comparison (Calabrese et al, 2007).

There is limited evidence from case series for the role of immunomodulator therapy, such as azathioprine and 6-mercaptopurine, in patients with microscopic colitis. One case series included 46 patients who were budesonide intolerant, budesonide dependent or those experiencing frequent relapse after short-term budesonide treatment (Münch et al, 2013b). Those intolerant to azathioprine were switched to 6-mercaptopurine, resulting in clinical remission in a total of 19 patients (41%) overall in the study. In two small case series (Münch et al, 2013b; Cotter et al, 2017) adverse effects were common, resulting in cessation of therapy in 35% and 67% of patients respectively. The data for methotrexate are inconclusive and limited to small case series. One retrospective study suggested a clinical response to low dose methotrexate in budesonide-naïve patients with collagenous colitis (Riddell et al, 2007), while a case series of nine patients who were intolerant or non-responsive to budesonide demonstrated no benefit of methotrexate 15–25 mg given for 12 weeks (Münch et al, 2013a).

Biological therapy has been used in refractory cases of microscopic colitis, although again the evidence is extremely limited to case series where anti-tumour necrosis factor agents, infliximab and adalimumab, have been reported as being effective (Münch et al, 2012b; Daferera et al, 2019). More recently, successful clinical responses to vedolizumab, a gut-selective, anti-integrin agent, have been reported, including a case report of collagenous colitis which was refractory to budesonide and a case series of eleven patients from Europe and Canada with microscopic colitis (Cushing et al, 2018; Rivière et al, 2019). In the case series, nine patients had failed one immunosuppressant and ten patients had microscopic

Key points

- The incidence of microscopic colitis is rising.
- Symptoms are related to poor health-related quality of life but prognosis is good so microscopic colitis must be considered in the differential diagnosis of chronic non-bloody diarrhoea.
- There is no reliable biomarker so colonoscopy and biopsies remain the mainstay of diagnosis; microscopic findings can be patchy so biopsies should be taken from each segment.
- Even with normal faecal calprotectin levels, consider colonoscopy and biopsy in patients over 50 years of age with persistent symptoms to exclude microscopic colitis.
- Colonoscopy is usually macroscopically normal but some endoscopic findings may be suggestive of microscopic colitis.
- Budesonide is the considered first-line therapy in patients with microscopic colitis at 9 mg once daily for 6–8 weeks.
- In cases of relapse, low-dose budesonide (3–6 mg) can be considered for maintenance therapy.
- Further research is required to better understand pathophysiology, identify clinical biomarkers and evaluate therapeutic options for budesonide refractory disease.

colitis that was refractory to previous anti-tumour necrosis factor therapy. Three infusions of vedolizumab resulted in clinical remission in five patients.

Surgery has been limited to severe medical refractory cases, with reports in the literature of subtotal colectomy and diverting ileostomy being performed (Järnerot et al, 1995).

Conclusions

Microscopic colitis is a common chronic inflammatory disease and a major cause of persistent non-bloody watery diarrhoea, particularly in elderly women. Diagnosis is based on histopathology, with biopsies ideally being taken from colonic segments during colonoscopy. Other common causes of chronic diarrhoea, such as coeliac disease and bile acid malabsorption, should be excluded. Exacerbating factors such as smoking and potential offending drugs such as non-steroidal anti-inflammatory drugs and proton pump inhibitors should be avoided. Budesonide is the only drug with strong randomised controlled trial evidence in microscopic colitis and therefore should be first-line therapy. The authors recommend starting with 9 mg once daily for 6–8 weeks. Reassessment is crucial in the case of relapse; if relapse is confirmed then re-treatment with budesonide is recommended followed by a low dose (3–6 mg daily) for maintenance. Refractory cases with no response to budesonide should be carefully evaluated by a specialist and other medical therapies such as biologics can be cautiously considered, although the level of supporting evidence is low quality. Although microscopic colitis is gaining more recognition, it is still under-recognised by clinicians and efforts are required to increase awareness. It is a disease that is ripe for further research, with further insights required into disease pathogenesis, and ideally identification of clinical biomarkers. Further data are needed for therapeutic options, particularly in maintenance of chronic disease, including addressing long-term risks and benefits for budesonide therapy, and high-quality studies to evaluate agents such as immunomodulators and biologics for refractory cases.

Author details

[1]Department of Gastroenterology, University College Hospital, London, UK

[2]Department of Gastroenterology, St Mark's Hospital, LNWH Trust, Harrow, UK

[3]Department of Surgery, Imperial College London, London, UK

Conflicts of interest

AA has received lecture fees from MSD, Abbvie, Dr Falk, Shire, Allergan, Janssen, Takeda, Vifor Pharma; OFA: none.

References

Baert F, Schmit A, D'Haens G et al. Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. Gastroenterology. 2002;122(1):20–25. https://doi.org/10.1053/gast.2002.30295

Beaugerie L, Pardi DS. Review article: drug-induced microscopic colitis – proposal for a scoring system and review of the literature. Aliment Pharmacol Ther. 2005;22(4):277–284. https://doi.org/10.1111/j.1365-2036.2005.02561.x

Bohr J, Tysk C, Eriksson S et al. Collagenous colitis: a retrospective study of clinical presentation and treatment in 163 patients. Gut. 1996;39(6):846–851. https://doi.org/10.1136/gut.39.6.846

Bonderup OK, Hansen JB, Birket-Smith L et al. Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. Gut. 2003;52(2):248–251. https://doi.org/10.1136/gut.52.2.248

Bonderup OK, Hansen JB, Teglbjaerg PS et al. Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. Gut. 2009;58(1):68–72. https://doi.org/10.1136/gut.2008.156513

Calabrese C, Fabbri A, Areni A et al. Mesalazine with or without cholestyramine in the treatment of microscopic colitis: randomized controlled trial. J Gastroenterol Hepatol. 2007;22(6):809–814. https://doi.org/10.1111/j.1440-1746.2006.04511.x

Cotter TG, Kamboj AK, Hicks SB et al. Immune modulator therapy for microscopic colitis in a case series of 73 patients. Aliment Pharmacol Ther. 2017;46(2):169–174. https://doi.org/10.1111/apt.14133

Cushing KC, Mino-Kenudson M, Garber J, Lochhead P, Khalili H. Vedolizumab as a novel treatment for refractory collagenous colitis: a case report. Am J Gastroenterol. 2018;113(4):632–633. https://doi.org/10.1038/ajg.2018.7

Daferera N, Hjortswang H, Ignatova S et al. Single-centre experience with anti-tumour necrosis factor treatment in budesonide-refractory microscopic colitis patients. United European Gastroenterol J. 2019;7(9):1234–1240. https://doi.org/10.1177/2050640619871750

Fernandez-Bañares F, Esteve M, Salas A et al. Bile acid malabsorption in microscopic colitis and in previously unexplained functional chronic diarrhea. Dig Dis Sci. 2001;46(10):2231-2238. https://doi.org/10.1023/a:1011927302076

Fernández-Bañares F, de Sousa MR, Salas A, et al. Epidemiological risk factors in microscopic colitis: a prospective case-control study. Inflamm Bowel Dis. 2013;19(2):411-417. https://doi.org/10.1002/ibd.23009

Fine K, Ogunji F, Lee E et al. Randomized, double-blind, placebo-controlled trial of bismuth subsalicylate for microscopic colitis. Gastroenterology. 1999;116:A880

Järnerot G, Tysk C, Bohr J et al. Collagenous colitis and fecal stream diversion. Gastroenterology. 1995;109(2):449–455. https://doi.org/10.1016/0016-5085(95)90332-1

Koulaouzidis A, Saeed AA. Distinct colonoscopy findings of microscopic colitis: not so microscopic after all? World J Gastroenterol. 2011;17(37):4157-4165. https://doi.org/10.3748/wjg.v17.i37.4157

Koulaouzidis A, Yung DE, Nemeth A et al. Macroscopic findings in collagenous colitis: a multi-center, retrospective, observational cohort study. Ann Gastroenterol. 2017;30(3):309-314. https://doi.org/10.20524/aog.2017.0131

Langner C, Aust D, Ensari A et al. Histology of microscopic colitis-review with a practical approach for pathologists. Histopathology. 2015;66(5):613-626. https://doi.org/10.1111/his.12592

Lazenby AJ, Yardley JH, Giardiello FM et al. Lymphocytic ("microscopic") colitis: a comparative histopathologic study with particular reference to collagenous colitis. Hum Pathol. 1989;20(1):18-28. https://doi.org/10.1016/0046-8177(89)90198-6

Lindström CG. 'Collagenous colitis' with watery diarrhoea--a new entity? Pathol Eur. 1976;11(1):87–89

Liszka Ł, Woszczyk D, Pajak J. Histopathological diagnosis of microscopic colitis. J Gastroenterol Hepatol. 2006;21(5):792–797. https://doi.org/10.1111/j.1440-1746.2006.04332.x

Miehlke S, Heymer P, Bethke B et al. Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicenter trial. Gastroenterology. 2002;123(4):978–984. https://doi.org/10.1053/gast.2002.36042

Miehlke S, Madisch A, Bethke B et al. Oral budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2008;135(5):1510–1516. https://doi.org/10.1053/j.gastro.2008.07.081

Miehlke S, Madisch A, Karimi D et al. Budesonide is effective in treating lymphocytic colitis: a randomized double-blind placebo-controlled study. Gastroenterology. 2009;136(7):2092–2100. https://doi.org/10.1053/j.gastro.2009.02.078

Miehlke S, Madisch A, Kupcinskas L et al. Budesonide is more effective than mesalamine or placebo in short-term treatment of collagenous colitis. Gastroenterology. 2014;146(5):1222–1230.e2. https://doi.org/10.1053/j.gastro.2014.01.019

Miehlke S, Aust D, Mihaly E et al. Efficacy and safety of budesonide, vs mesalazine or placebo, as induction therapy for lymphocytic colitis. Gastroenterology. 2018;155(6):1795–1804.e3. https://doi.org/10.1053/j.gastro.2018.08.042

Miehlke S, Verhaegh B, Tontini GE et al. Microscopic colitis: pathophysiology and clinical management. Lancet Gastroenterol Hepatol. 2019;4(4):305–314. https://doi.org/10.1016/S2468-1253(19)30048-2

Münch A, Aust D, Bohr J et al. Microscopic colitis: current status, present and future challenges: statements of the European Microscopic Colitis Group. J Crohns Colitis. 2012a;6(9):932–945. https://doi.org/10.1016/j.crohns.2012.05.014

Münch A, Ignatova S, Ström M. Adalimumab in budesonide and methotrexate refractory collagenous colitis. Scand J Gastroenterol. 2012b;47(1):59–63. https://doi.org/10.3109/00365521.2011.639079

Münch A, Bohr J, Vigren L et al. Lack of effect of methotrexate in budesonide-refractory collagenous colitis. Clin Exp Gastroenterol. 2013a;6:149–152. https://doi.org/10.2147/CEG.S48201

Münch A, Fernandez-Banares F, Munck LK. Azathioprine and mercaptopurine in the management of patients with chronic, active microscopic colitis. Aliment Pharmacol Ther. 2013b;37(8):795–798. https://doi.org/10.1111/apt.12261

Münch A, Bohr J, Miehlke S et al. Low-dose budesonide for maintenance of clinical remission in collagenous colitis: a randomised, placebo-controlled, 12-month trial. Gut. 2016;65(1):47–56. https://doi.org/10.1136/gutjnl-2014-308363

Nguyen GC, Smalley WE, Vege SS et al. American Gastroenterological Association Institute guideline on the medical management of microscopic colitis. Gastroenterology. 2016;150(1):242–246. https://doi.org/10.1053/j.gastro.2015.11.008

Nyhlin N, Wickbom A, Montgomery SM et al. Long-term prognosis of clinical symptoms and health-related quality of life in microscopic colitis: a case-control study. Aliment Pharmacol Ther. 2014;39(9):963–972. https://doi.org/10.1111/apt.12685

Olesen M, Eriksson S, Bohr J et al. Lymphocytic colitis: a retrospective clinical study of 199 Swedish patients. Gut. 2004;53(4):536–541. https://doi.org/10.1136/gut.2003.023440

Pardi DS, Loftus EV, Tremaine WJ et al. T1193 a randomized, double-blind, placebo-controlled trial of budesonide for the treatment of active lymphocytic colitis. Gastroenterology. 2009;136(5):A-519–A-520. https://doi.org/10.1016/S0016-5085(09)62392-1

Pisani LF, Tontini GE, Marinoni B, et al. Biomarkers and Microscopic Colitis: An Unmet Need in Clinical Practice. Front Med (Lausanne). 2017;4:54. https://doi.org/10.3389/fmed.2017.00054

Riddell J, Hillman L, Chiragakis L et al. Collagenous colitis: oral low-dose methotrexate for patients with difficult symptoms: long-term outcomes. J Gastroenterol Hepatol. 2007;22(10):1589–1593. https://doi.org/10.1111/j.1440-1746.2007.05128.x

Rivière P, Münch A, Michetti P et al. Vedolizumab in refractory microscopic colitis: an international case series. J Crohns Colitis. 2019;13(3):337–340. https://doi.org/10.1093/ecco-jcc/jjy169

Sebastian S, Wilhelm A, Jessica L et al. Budesonide treatment for microscopic colitis: systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31(8):919–927. https://doi.org/10.1097/MEG.0000000000001456

Thijs WJ, van Baarlen J, Kleibeuker JH et al. Microscopic colitis: prevalence and distribution throughout the colon in patients with chronic diarrhoea. Neth J Med. 2005;63(4):137–140

Tong J, Zheng Q, Zhang C et al. Incidence, prevalence, and temporal trends of microscopic colitis: a systematic review and meta-analysis. Am J Gastroenterol. 2015;110(2):265–277. https://doi.org/10.1038/ajg.2014.431

Tripathi K, Dunzendorfer T. Budesonide-related iatrogenic Cushing's syndrome in microscopic colitis. ACG Case Rep J. 2017;4:e5. https://doi.org/10.14309/crj.2017.5