

Microscopic colitis: A therapeutic challenge

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on the single patient, appears to be the most sensible option.

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Abstract

The treatment of microscopic colitis is mainly based on the use of budesonide, the only drug found effective in controlled clinical trials. After an initial course at a dose of 9 mg daily, however, most patients relapse when the drug is discontinued, hence a maintenance therapy at doses of 6 mg daily or lower is necessary. In order to avoid steroid dependence and drug toxicity different pharmacological agents should be considered as an alternative to indefinite long-term budesonide treatment. Evidence-based guidelines are currently lacking due to the lack of conclusive data concerning the use of either immunosuppressive or anti-tumor necrosis factor agents. For the time being in clinical practice the skilled physician should therefore tailor long term management of microscopic colitis on the single patient.

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Key words: Microscopic colitis; Budesonide; Mesalazine; Immunosuppressants

Core tip: The efficacy of short-term treatment of microscopic colitis with budesonide is confirmed. Long-term therapy is not advisable because of possible side effects, but the efficacy of alternative drugs such as immunosuppressants or anti-tumor necrosis factor agents remains to be established. For the time being prolonged budesonide treatment in minimal doses, tailored

MICROSCOPIC COLITIS

Microscopic colitis (MC) is an intestinal inflammatory disorder the diagnosis of which relies on specific histopathological findings, namely an increased number of lymphocytes in the colonic epithelium and of subepithelial chronic inflammatory cells (lymphocytic colitis), in some cases with a thickening of the subepithelial layer (collagenous colitis)^[1,2].

Radiographic and endoscopic features are constantly normal. The main symptom is chronic watery diarrhea without bleeding, the disease being more common among older individuals, especially of female gender. Although a genetic cause has not been proven, familial occurrence has been reported.

Smoking is a risk factor and bile acid malabsorption is frequent (however, a bile acid binding drug such as cholestyramine may improve symptoms but not histopathology)^[1-3].

Medications such as nonsteroidal antiinflammatory drugs, proton pump inhibitor, ticlopidine, sertraline *etc.* can induce MC^[4]. Hence, accurate information about pharmacological treatment history is mandatory in order to discontinue the supposedly responsible drug.

The only medication found effective in randomized, placebo-controlled trials is budesonide, which, at a dose of 9 mg per day is able to induce clinical remission and histological improvement in about 81% of cases^[5]. The superior efficacy of budesonide compared with placebo has been shown in four controlled trials involving patients with either collagenous or lymphocytic form of MC^[6-9].

By contrast only a small trial comparing prednisolone and placebo for two weeks reported a trend toward clinical response^[10]. At any rate, budesonide should be preferred to other steroids not only because of fewer side effects, but also because the success rate is higher and the incidence of clinical relapses is lower^[11,12].

When budesonide is withdrawn, symptomatic relapse of MC can occur in 60%-80% of cases^[13,14]. In order to maintain remission budesonide can be successfully administered at a dose of 6 mg daily, up to six months^[14,15]. After that period there is no published evidence that the drug continues to be effective, but clinical practice shows that budesonide 3-6 mg daily can prevent recurrence, although patients become at risk of becoming steroid dependent and to develop side effects due to long-term steroid therapy. The minimum dose of budesonide should be employed, even 3 mg every other day being occasionally sufficient to maintain clinical remission (Guslandi M, unpublished data), but in order to avoid steroid dependence and drug toxicity other therapeutic options must be considered.

Mesalazine, which is usually well tolerated, would represent an ideal long-term treatment, but evidence of its efficacy in MC is weak, retrospective series reporting benefit in fewer than half the patients as a short term therapy while data for periods exceeding 6 mo are lacking^[16,17].

Immunosuppressive agents can be taken into consideration, both in patients with severe symptoms who do not respond to full doses of budesonide or who are experiencing side effects and/or steroid dependence during long-term budesonide treatment. Unfortunately available data with either azathioprine (or 6-mercaptopurine) and methotrexate in MC are extremely limited and inconclusive^[18-20] despite their not infrequent use in clinical practice by gastroenterologists.

In the attempt to avoid colectomy in severe cases of MC refractory to any other pharmacological treatment, the possible use of biological agents has been tested, with promising results^[21,22] but more conclusive data are needed.

Thus, long-term management of microscopic colitis remains elusive, especially in patients refractory or intolerant to budesonide, but even in subjects where the drug is effective but continuous intake for an indefinite length of time is not advisable. In those cases physicians must take therapeutic decisions irrespective of evidence-based data, tailoring the treatment on the characteristics and needs of the single patient. Even a recent treatment algorithm proposed by the European Microscopic Colitis Group^[23] includes drugs such as loperamide, mesalazine, cholestyramine and bismuth, the efficacy of which is questionable and uncertain, pointing out the fact that the use of those medication is empirical. The same applies to immunosuppressants and anti-tumor necrosis factor agents, although the former, in spite of the scarce controlled data, appear to be a sensible and comparatively safe approach. Needless to say, randomized, controlled

studies with azathioprine or methotrexate are eagerly awaited and sorely needed.

REFERENCES

- 1 Pardi DS, Smyrk TC, Tremaine WJ, Sandborn WJ. Microscopic colitis: a review. *Am J Gastroenterol* 2002; **97**: 794-802 [PMID: 12003412 DOI: 10.1111/j.1572-0241.2002.05595.x]
- 2 Pardi DS, Kelly CP. Microscopic colitis. *Gastroenterology* 2011; **140**: 1155-1165 [PMID: 21303675 DOI: 10.1053/j.gastro.2011.02.003]
- 3 Chetty R, Govender D. Lymphocytic and collagenous colitis: an overview of so-called microscopic colitis. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 209-218 [PMID: 22349169 DOI: 10.1038/nrgastro.2012.16]
- 4 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**: 277-284 [PMID: 16097993 DOI: 10.1111/j.1365-2036.2005.02561.x]
- 5 Chande N, MacDonald JK, McDonald JW. Interventions for treating microscopic colitis: a Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Review Group systematic review of randomized trials. *Am J Gastroenterol* 2009; **104**: 235-241; quiz 234, 242 [PMID: 19098875 DOI: 10.1038/ajg.2008.16]
- 6 Miehke S, Heymer P, Bethke B, Bästlein E, Meier E, Bartram HP, Wilhelms G, Lehn N, Dorta G, DeLarive J, Tromm A, Bayerdörffer E, Stolte M. Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicenter trial. *Gastroenterology* 2002; **123**: 978-984 [PMID: 12360457]
- 7 Bonderup OK, Hansen JB, Birket-Smith L, Vestergaard V, Teglbjaerg PS, Fallingborg J. Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. *Gut* 2003; **52**: 248-251 [PMID: 12524408 DOI: 10.1136/gut.52.2.248]
- 8 Baert F, Schmit A, D'Haens G, Dedeurwaerdere F, Louis E, Cabooter M, De Vos M, Fontaine F, Naegels S, Schurmans P, Stals H, Geboes K, Rutgeerts P. Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. *Gastroenterology* 2002; **122**: 20-25 [PMID: 11781276 DOI: 10.1053/gast.2002.30295]
- 9 Miehke S, Madisch A, Karimi D, Wonschik S, Kuhlisch E, Beckmann R, Morgner A, Mueller R, Greinwald R, Seitz G, Baretton G, Stolte M. Budesonide is effective in treating lymphocytic colitis: a randomized double-blind placebo-controlled study. *Gastroenterology* 2009; **136**: 2092-2100 [PMID: 19303012 DOI: 10.1053/j.gastro.2009.02.078]
- 10 Munck LK, Kjeldsen J, Philipsen E, Fischer Hansen B. Incomplete remission with short-term prednisolone treatment in collagenous colitis: a randomized study. *Scand J Gastroenterol* 2003; **38**: 606-610 [PMID: 12825868 DOI: 10.1080/0036.55.2031.0002210]
- 11 Stewart MJ, Seow CH, Storr MA. Prednisolone and budesonide for short- and long-term treatment of microscopic colitis: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2011; **9**: 881-890 [PMID: 21699817 DOI: 10.1016/j.cgh]
- 12 Gentile NM, Abdalla AA, Khanna S, Smyrk TC, Tremaine WJ, Faubion WA, Kammer PP, Sandborn WJ, Loftus EV, Pardi DS. Outcomes of patients with microscopic colitis treated with corticosteroids: a population-based study. *Am J Gastroenterol* 2013; **108**: 256-259 [PMID: 23295275 DOI: 10.1038/ajg.2012.416]
- 13 Bonderup OK, Hansen JB, Teglbjaerg PS, Christensen LA, Fallingborg JF. Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. *Gut* 2009; **58**: 68-72 [PMID: 18669576 DOI: 10.1136/gut.2008.156513]

- 14 **Miehlke S**, Madisch A, Voss C, Morgner A, Heymer P, Kuhlisch E, Bethke B, Stolte M. Long-term follow-up of collagenous colitis after induction of clinical remission with budesonide. *Aliment Pharmacol Ther* 2005; **22**: 1115-1119 [PMID: 16305725]
- 15 **Miehlke S**, Madisch A, Bethke B, Morgner A, Kuhlisch E, Henker C, Vogel G, Andersen M, Meier E, Baretton G, Stolte M. Oral budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2008; **135**: 1510-1516 [PMID: 18926826 DOI: 10.1053/j.gastro.2008.07.081]
- 16 **Calabrese C**, Fabbri A, Areni A, Zahlane D, Scialpi C, Di Febo G. Mesalazine with or without cholestyramine in the treatment of microscopic colitis: randomized controlled trial. *J Gastroenterol Hepatol* 2007; **22**: 809-814 [PMID: 17565633 DOI: 10.1111/j.1440-1746.2006.04511.x]
- 17 **Yen EF**, Pardi DS. Review of the microscopic colitides. *Curr Gastroenterol Rep* 2011; **13**: 458-464 [PMID: 21773709 DOI: 10.1007/s11894-011-0207-7]
- 18 **Pardi DS**, Loftus EV, Tremaine WJ, Sandborn WJ. Treatment of refractory microscopic colitis with azathioprine and 6-mercaptopurine. *Gastroenterology* 2001; **120**: 1483-1484 [PMID: 11313319 DOI: 10.1053/gast.2001.23976]
- 19 **Vennamaneni SR**, Bonner GF. Use of azathioprine or 6-mercaptopurine for treatment of steroid-dependent lymphocytic and collagenous colitis. *Am J Gastroenterol* 2001; **96**: 2798-2799 [PMID: 11569721 DOI: 10.1111/j.1572-0241.2001.04145.x]
- 20 **Riddell J**, Hillman L, Chiragakis L, Clarke A. Collagenous colitis: oral low-dose methotrexate for patients with difficult symptoms: long-term outcomes. *J Gastroenterol Hepatol* 2007; **22**: 1589-1593 [PMID: 17845686 DOI: 10.1111/j.1440-1746.2007.05128.x]
- 21 **Münch A**, Ignatova S, Ström M. Adalimumab in budesonide and methotrexate refractory collagenous colitis. *Scand J Gastroenterol* 2012; **47**: 59-63 [PMID: 22149977 DOI: 10.3109/00365521.2011.639079]
- 22 **Esteve M**, Mahadevan U, Sainz E, Rodriguez E, Salas A, Fernández-Bañares F. Efficacy of anti-TNF therapies in refractory severe microscopic colitis. *J Crohns Colitis* 2011; **5**: 612-618 [PMID: 22115383 DOI: 10.1016/j.crohns.2011.05.001]
- 23 **Münch A**, Aust D, Bohr J, Bonderup O, Fernández Bañares F, Hjortswang H, Madisch A, Munck LK, Ström M, Tysk C, Miehlke S. Microscopic colitis: Current status, present and future challenges: statements of the European Microscopic Colitis Group. *J Crohns Colitis* 2012; **6**: 932-945 [PMID: 22704658 DOI: 10.1016/j.crohns.2012.05.014]

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