

## Microscopic colitis: A therapeutic challenge

Mario Guslandi

Mario Guslandi, Gastroenterology Unit, S. Raffaele University Hospital, 20132 Milan, Italy

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Correspondence to: Mario Guslandi, MD, FACP, Professor, Gastroenterology Unit, S. Raffaele University Hospital, Via Olgettina 60, 20132 Milan, Italy. [guslandi.mario@hsr.it](mailto:guslandi.mario@hsr.it)

Telephone: +39-2-26432744 Fax: +39-2-26433491

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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

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

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### 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)<sup>[1,2]</sup>.

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)<sup>[1-3]</sup>.

Medications such as nonsteroidal antiinflammatory drugs, proton pump inhibitor, ticlopidine, sertraline *etc.* can induce MC<sup>[4]</sup>. 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<sup>[5]</sup>. 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<sup>[6-9]</sup>.

By contrast only a small trial comparing prednisolone and placebo for two weeks reported a trend toward clinical response<sup>[10]</sup>. 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<sup>[11,12]</sup>.

When budesonide is withdrawn, symptomatic relapse of MC can occur in 60%-80% of cases<sup>[13,14]</sup>. In order to maintain remission budesonide can be successfully administered at a dose of 6 mg daily, up to six months<sup>[14,15]</sup>. 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<sup>[16,17]</sup>.

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<sup>[18-20]</sup> 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<sup>[21,22]</sup> 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<sup>[23]</sup> 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.

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