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REVIEW

Advances in knowledge on microscopic colitis: From bench to bedside

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ABSTRACT

Microscopic colitis (MC) is a general term that describes a family of chronic inflammatory bowel diseases, including lymphocytic colitis (LC) and collagenous colitis (CC). The two forms are characterized by chronic watery diarrhea with normal or near normal endoscopic colonic appearance and specific histopathological abnormalities. Data from recent epidemiological studies reported the diagnosis of MC from several different regions in the world, providing that it can be a worldwide condition. The etiopathogenesis of MC still remains unknown but it is generally accepted that MC is a multifactorial disease, probably secondary to an abnormal immune reaction in predisposed individuals, triggered by different luminal factors (infections, drugs, autoimmunity and/or bile acids). Furthermore, some studies show that the epithelial barrier function in the colonic mucosa of MC patients is also impaired. Several mucosal factors of intestinal inflammation have been studied in MC, postulating that an aberrant T-lymphocyte response may lead to a chronic gut inflammatory condition, with the infiltration of colonic mucosa by different proportion of subset of T-lymphocytes. Little is known about the specific inflammatory mediators in MC pathogenesis, but a predominant Th1 type cytokine profile has been demonstrated. Currently, a number of medical treatments have been studied in MC patients, following mainly an empirical treatment approach. Further studies are needed in order to obtain prospective and more evidence-based data. In the future, it will be possible to develop causal treatment approaches after better understanding the molecular mechanisms behind the origin of the disease.

Key words: Microscopic colitis. Lymphocytic colitis. Collagenous colitis. Pathogenesis. Therapeutics. T-lymphocytes.

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List of abbreviations: MC: Microscopic colitis, LC: Lymphocytic colitis; CC: Collagenous colitis; IBS: Irritable bowel syndrome; BAM: Bile acid malabsorption; iNOS: Inducible nitric oxide synthase; NO: Nitric oxide; EC: Enterochromaffin cells; CTLs: Cytotoxic T lymphocytes; IL-2: Interleukin-2; Treg: Regulatory T-cells; IL-10: Interleukin-10; TGF-beta: Transforming growth factor-beta; IFN-gama: Interferon-gama; TNF-alpha: Tumor necrosis factor-alpha; NF-KB: Nuclear factor-KB; IL-17: Interleukin-17; HLA: Human leucocyte antigen; CD: Celiac disease; IL-6: Interleukin-6; IL-1b: Interleukin-1b; IL-1RA: Interleukin-1RA; 5-ASA: 5-aminosalycilic acid.

INTRODUCTION

Microscopic colitis (MC) is a general term, used from 1980 (1) that describes a family of chronic inflammatory bowel diseases, including the two main entities, lymphocytic colitis (LC) and collagenous colitis (CC). The two forms are characterized by chronic or intermittent watery diarrhea, with normal o near normal endoscopic colonic appearance and specific microscopic abnormalities in the colonic mucosa, which allow to distinguish one form to the other. It is not clear whether LC and CC are the same disease entity, or have to be considered as different stages of the same condition (2,3). MC is a fairly new disease that is not always considered in patients with watery chronic diarrhea, because the diagnosis of MC may still be overlooked or misdiagnosed as irritable bowel syndrome (IBS). Epidemiological studies show that MC is diagnosed in up to 10 % of patients investigated for chronic or intermittent watery non-bloody diarrhea and in more than 20 % of patients older than 70 year old, being more frequent in elderly women and smokers (4). Data from recent epidemiological studies reported the diagnosis of MC from several different regions in the world, making it a worldwide condition. Nowadays, after a period of generally rising incidence of MC, data from recent epidemiological studies, show incidence rates ranging between < 1/100.000 to 10.8/100.000 inhabit-

ants for CC and between 2.1/100.000 to 18.9/100.000 inhabitants for LC (5-19) (Table I). The pathogenesis of MC still remains unknown, but it is considered to be multifactorial, showing the importance of an impaired mucosal barrier function and the interaction between luminal content (including from bacteria to drugs) and the mucosal intestinal immune system. A better understanding of the immunological basis of inflammation in the colonic mucosa could lead to better therapeutic options and the design of new strategies to treat MC patients in the future.

METHODS

This paper reviews the current evidences on the pathogenetic mechanisms underlying MC and its implications in the therapeutic management of the disease. We searched the PubMed, Cochrane, MEDLINE, and Scopus libraries, using the following individual and combined key words: Microscopic colitis; collagenous colitis; lymphocytic colitis; treatment or therapy; etiology; pathophysiology; genetic factors; luminal factors; epithelial barrier function; mediators of intestinal inflammation; budesonide; mesalazine; loperamide; bismuth subsalicylate; probiotics; immunosuppressive therapy; anti-TNF treatment. Reference lists in the articles obtained were also searched in order to identify other potential sources of information. The results were limited only to studies published, written in English.

Etiopathogenetic mechanisms of MC

It is generally accepted that MC is a multifactorial disease, probably secondary to an abnormal immune reaction that appears in predisposed individuals, triggered by different luminal factors (infections, drugs, autoimmunity and/or bile acids). The mechanism by which the alteration of the mucosal immune response generates the dominant symptom of the disease (diarrhea) is still under investigation, with several data showing that the diarrhea in MC patients could have an inflammatory origin. Indeed, the severity of diarrhea seems to be associated with the intensity of inflammation in the lamina propria in LC, while in patients with CC is not correlated to the thickness of the collagenous band (20). Furthermore, in those patients with CC, who had a temporary ileostomy, the recurrence of inflammation in the lamina propria was the first histological change observed in the development of the symptomatic disease (21). Nonetheless, other data indicate that osmotic and secretory components could also contribute to the development of diarrhea in MC patients. In fact, fasting can reduce the diarrhea (22) and some authors have demonstrated that diarrhea can be originated from a reduced Na^+ and Cl^- absorption, together with an active chloride secretion (23,24). Recently, a study from colonic biopsies from patients with CC and LC has shown that electrogenic sodium transport diminished and the epithelial resistance decreased. Finally, unlike patients with IBS, there are no signs of visceral hypersensitivity in patients with CC, also showing a normal ano-rectal function, de-

Table I. Distribution by region and study period of the annual incidence per 100,000 inhabitants in population-based epidemiological studies of lymphocytic colitis and collagenous colitis

Region (country)	*Study period*	*CC incidence*	*LC incidence*
Örebro (Sweden) (5)	1989-1993	2.7	---
Örebreo (Sweden) (6)	1993-1995	3.7	3.1
Örebro (Sweden) (6)	1996-1998	6.1	5.7
Örebro (Sweden) (7)	1999-2003	4.7	5.1
Örebro (Sweden) (7)	2004-2008	5.8	4.5
Lund (Sweden) (8)	2001-2010	5.4	---
Uppsala (Sweden) (9)	2005-2009	7	4.8
Reykjavik (Iceland) (10)	1995-1999	5.2	4.0
Terrassa (Spain) (11)	1993-1997	1.1	3.1
Terrassa (Spain) (12)	2004-2008	2.6	2.1
Tomelloso (Spain) (13)	2008-2010	< 1	16
Zeeland (Denmark) (14)	2002-2010	10.8	6.7
Olmsted (USA) (15)	1985-1997	1.6	2.7
Olmsted (USA) (15)	1998-2001	7.1	12.6
Olmsted (USA) (16)	2002-2010	9.1	12
Calgary (Canada) (17)	2002-2004	4.6	5.4
Calgary (Canada) (18)	2004-2008	6.7-7.9	10.1-18.9
Calgary (Canada) (19)	2004-2008	7.2	14

CC: Collagenous colitis, LC: Lymphocyte colitis, USA: United States of America. Adapted from Münch et al. (4).

spite the presence of rectal inflammation (25). Therefore, a combination of several factors may contribute to the induction and maintenance of an inflammatory response in the colonic mucosa of patients with MC to produce the symptoms of the disease (Fig. 1), which we will describe in detail in the following sections.

Luminal factors

Several luminal factors have been studied as putative triggers, to induce an impaired inflammatory mucosa response in MC patients:

Firstly, an infectious etiology is proposed, despite no specific pathogen has been identified until now. Some studies show the onset of MC following a gastrointestinal infections, as in the case of a *Clostridium difficile* infection, that can catalyze the inflammatory response to induce the development of CC (26), or the observation that serum antibodies against to *Yersinia enterocolitica* were more common among CC patients compared to controls, leading to the speculation of a previous *Yersinia enterocolitica* infection triggering the development of the disease (27). A role for gastrointestinal infections in the pathogenesis of MC is strikingly resembling to the hypothesis of post-infectious IBS (28), with similar clinical presentation, spontaneous regression and similar histological changes (intraepithelial and submucosal infiltration by lymphocytes and mast cells) (29).

Secondly, it is widely known that colonic infusion of bile acids may determine colitis in animal models (30), and in patients with ileal resection, with subsequent bile acid malabsorption (BAM), may have diarrhea (31). Some small retrospective case series have found BAM to be presented in up to 60 % of patients with LC and in up to 44 % of those with CC (32,33). This suggests that, at least in some patients, BAM might have a key role in the development of the disease. However, the evidence on the role of bile acids in the pathogenesis of MC is still conflicting. In fact, small studies conducted with bile acid breath test showed little or no evidence of BAM in MC patients (34-36) and an association between cholecystectomy and MC has not been found (37). On the other hand, some studies investigating the retention of selenium homocholyltaurine have found variable degrees of BAM (31,38) and bile acid binding treatment, such as using cholestyramine, has been shown to be effective in CC patients. Finally, a recent study has shown that a low concentration of dihydroxy bile acids can aggravate the mucosal barrier dysfunction in CC patients by increasing the uptake of non-pathogenic bacteria (39). However, whether BAM is causative or not still remains questionable (40) and on the basis of the new evidence, BAM and MC are probably associated but independent diseases.

Thirdly, drug consumption has been considered as an environmental risk factor causing or triggering MC. The likelihood of a specific drug to trigger MC has been shown in an interesting paper (41); drug imputation was assessed by using a French algorithm and adding the bibliographic score, calculated by the number of previous reports of a similar drug-event association (42). Significant associations were reported between MC and certain drugs with a high likelihood in triggering the disease, including non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), Ranitidine, Sertraline, Clozapine, Acarbose, Aspirin (ASA), Ticlopidine, Flavonoid vein tonic drugs and Entacapone (41). However, it is important to highlight that only by a re-challenge protocol (this is, assessing disease remission after drug withdrawal and recurrence after new expositions) it is possible to truly confirm causality relationships between some drugs and the development of a disease. Data from drug re-challenges are available only for few drugs, including Acarbose, Cyclo 3 forte, Ranitidine, Lansoprazole and Omeprazole (43-47), and some of them are limited to clinical recurrence, with no available histological assessment. Therefore, the possible causative nature of these associations is a matter of ongoing discussion, also because many drugs and their metabolites can produce diarrhea by several different mechanisms. They can affect the colon directly, either through their pharmacological activity, or through idiosyncratic hypersensitivity reactions, or indirectly by altering the colonization of gastrointestinal microorganisms (4). Several drugs thought to be associated with MC are also known to be involved in the development of chronic or recurrent diarrhea as a side effect (48), further confusing the possible causal role of drugs in the development of the disease. In this way the association between the

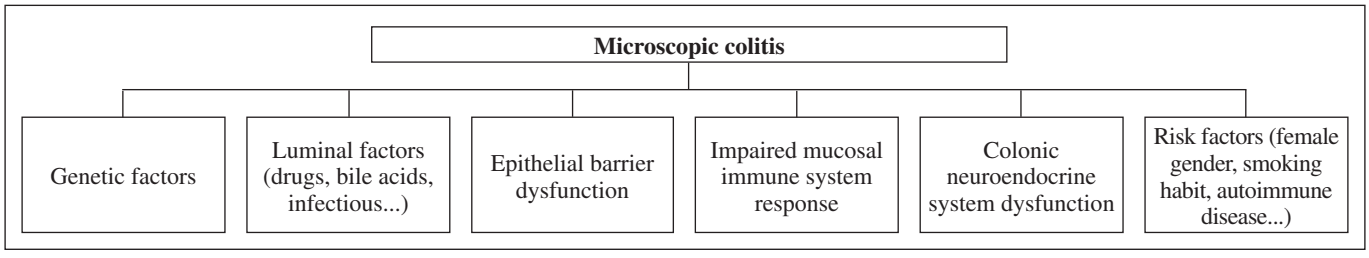

Fig. 1. A combination of several factors that produces and predisposes to the development of microscopic colitis.

development of MC and drug intake, could be considered as an idiosyncratic drug reaction and should be assessed before starting a specific treatment for MC.

Epithelial barrier dysfunction

The intestinal epithelium is a selective and regulated barrier that permits ions, water and nutrients to be absorbed, but restricts the passage of harmful molecules, bacteria, viruses and other pathogens (49). According with some studies, the colonic epithelial barrier function is impaired in MC patients, while the small bowel mucosa integrity remains still intact (50). In particular, we know that paracellular permeability is increased in CC patients, due to a reduced expression of occludin and claudin-4, which are important tight junction proteins, resulting in a reduction of the epithelial resistance (24). An *in vitro* study carried out over colonic biopsies from CC patients who were in clinical remission, found a significant dysfunction in the mucosal barrier associated with an increased transmucosal uptake of non-pathogenic bacteria. This worsened in case of an active disease and persisted despite effective treatment with budesonide (51). The diversion of the fecal stream by an ileostomy normalized the mucosal permeability and epithelial degeneration, in parallel with decreasing of the mucosal inflammation in CC patients. The altered mucosal permeability recurred after restoring the bowel continuity, and the thickened collagenous layer latter reappeared (52). Finally, increased levels of both inducible nitric oxide synthase (iNOS) and nitric oxide (NO) are also observed in the colonic mucosa of MC patients, which leads to an increased paracellular transit, by increasing the tight junction permeability (53-55). Some authors postulated that the increased levels of NO are caused by a higher secretion of serotonin from enterochromaffin (EC) cells, as observed in colonic mucosa samples from LC patients (56,57). The increase in colonic serotonin cell density probably results from the interaction between lymphocytes and EC cells. Serotonin accelerates the intestinal motility and promotes water and electrolyte secretion, with a secondary compensatory increased expression in peptide YY, as observed in LC patients (57). It in turn, inhibits prostaglandin E2 and vasoactive intestinal polypeptide activation, stimulating the absorption of water and electrolytes (58-60). This probably explains the intermittent evolution of the diarrhea in MC patients. However, it is not yet clear if mucosal barrier dysfunction is a primary or secondary phenomenon, underlying the mucosal inflammation (Fig. 2).

Impaired mucosal immune system

Several mucosal factors leading to intestinal inflammation have been studied in MC, postulating that an impaired adaptive immune response through aberrant T-cell responses leads to chronic gut inflammatory conditions (61). The number of CD3+ T-lymphocytes in the lamina propria and intraepithelial compartment is increased in LC and CC (62), as it is defined as a hallmark for these diseases. On the basis of immunohistochemical staining and flow cytometric analyses, most of the T lymphocytes are CD4+ within the lamina propria and CD8+ in intraepithelial compartment, carrying the alpha/beta form of the T-cell receptor (62), with a mixed Th17/Tc17 and Th1/Tc1 mucosal cytokine profile (63). The heavy infiltration by CD8+ cytotoxic T-lymphocytes (CTLs) in the colonic mucosa of MC patients has been recently shown to be due to an increased expansion of resident T-cells. It suggests that the activating antigen localizes in the colonic mucosa, such as demonstrated by a reduced T-cell receptor excision circles level with enhanced expression of Ki67+ T-cells in the colonic mucosa of MC patients (61,64). In fact, other studies have also demonstrated an

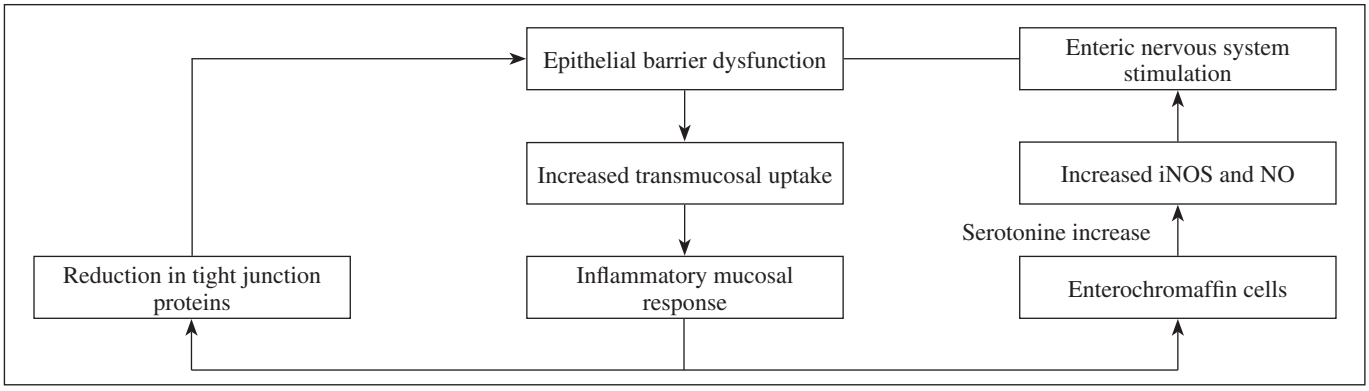

Fig. 2. Epithelial barrier dysfunction in microscopic colitis increases the transmucosal uptake of non-pathogen bacteria, and stimulates the inflammatory mucosal response, which in turn maintains the dysfunction through different but not completely known mechanisms. Among them, the reduction of the tight junction proteins (occludin and claudin-4) and the stimulation of enterochromaffin cells to secrete increased levels of serotonine. Serotonine increases intestinal motility and secretion through inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production.

elevated proportion of memory CD8+ T-cells (Ki67+ and CD45RO+ cells) in intraepithelial and lamina propria compartments, being more pronounced in CC than LC and in active disease, compared with the disease in histopathological remission state. It is important to highlight that compared to spleen memory T-cells, memory CD8+ T-cells can be more rapidly reactivated to produce uncontrolled or excessive cytotoxic activity against luminal antigens, developing and maintaining an intestinal chronic inflammatory response (64). Furthermore, CTLs induce proliferation of regulatory T-cells (Treg) through the secretion of interleukin (IL-2), which in turn inhibits CTLs-induced cytotoxic tissue damage, in order to maintain the self-tolerance status by the production of suppressor cytokines (IL-10, transforming growth factor [TGF]-beta) and by cell-to-cell contact-dependent mechanisms (65-68). CD25+FOXP3+ Treg are increased in the lamina propria of MC patients, probably blocking the spoiling effect of CTLs (69,70). In fact, this action is modulated by TGF-beta acting as a suppressive factor for inflammatory cells proliferation and function, with an additional role in causing the accumulation of collagen as observed in CC (71). Several additional factors are being studied as responsible causes in the formation of the thick subepithelial collagen band. Among others, increased numbers of activated subepithelial myofibroblasts (72,73) and vascular endothelial growth factor, which promote the accumulation of immature subepithelial matrix (74). In contrast, patients with LC have significant more CTLs than those with CC and less CD25+FOXP3 Treg than CC patients, although with increased levels compared to normal colonic mucosa (69). These observations support the theory that LC and CC could be considered as different stages of the same condition, with increased numbers of CTLs at the earliest stage (LC) and subepitelial collagen bands and increased CD25+FOXP3+ Treg in the later stage (CC) (69). Besides the lymphocytic infiltration, an increased number of eosinophils can be observed in the colonic mucosa of CC patients (75-77), along with increased levels of eosinophilic cationic protein (77) and degranulation of major basic protein (76), suggesting the involvement of the innate immune system in the pathogenesis of MC.

One report showed a predominant Th1-type cytokine profile, with marked increase in interferon (IFN)-gamma, IL-15 and iNOS expression and with lesser increase in tumor necrosis factor (TNF)-alpha (78). Increased activities of nuclear factor-KB (NF-KB), iNOS, IFN-gamma and COX-2, have been shown in other studies (79-82), especially in CC, where their increases were significantly higher than in LC. An increased expression of interleukin-17 (IL-17) in epithelial and inflammatory cells of MC patients has been recently demonstrated (63,83), which plays an important role in antimicrobial immunity at mucosal barriers and in the amplification of intestinal inflammatory responses.

Genetic factors

Whether genetic predisposition is of importance in MC is unclear. Several aspects in the sparse scientific evidences indicate that a genetic background could play a role in the etiology of MC. Familiar aggregation of MC cases were demonstrated in a Swedish study, which found five families with the occurrence of MC, with a sister-sister relationship, independently of smoking habits (84). Mother-daughter and father-son relationships have also been described (85,86).

Recently, a familial case of CC below 14 years old has been reported in a mother-daughter relationship (87). Unfortunately, until now, no concordance among twins has been reported for MC, pointing out that not only genetic predisposition, but also environmental factors, should also be considered in order to explain the familial occurrence of MC.

In addition, small studies have found an association between MC with various autoimmune-related human leukocyte antigens (HLA) haplotypes. An increasing prevalence of HLA-A1 and a decreased of HLA-A3 haplotypes has been found in LC, with no associated in CC patients (88). Some studies have reported on the association of MC with the HLA-DQ haplotypes predisposing to celiac disease (CD), with a prevalence level of HLA-DQ2 alleles up to 64 % of MC patients (among whom only 4 % had a concomitant CD), compared with only 31 % in control subjects (89). The association of HLA-DQ2 with LC without the association to CD has also been found (90).

Finally, different genetic polymorphisms have been studied in MC patients: the frequency of carriers for the GG allele of the SNP of matrix metalloproteinase was found significantly higher in CC patients than in healthy donors, being the odds ratio for an increased risk of CC 1,9 (95 % confidence interval [CI], 1, 3.5) (91). Unfortunately, the carrier frequencies of the alleles in SNP 8, 12 and 13 of *NOD2/CARD15* gene were not different between CC patients and healthy blood donors (92). The IL-6-174 gene polymorphism has also been related with MC, showing that the IL-6 GG and G genotypes were more frequent in patients with MC compared to controls, being the odds ratio of 1.5 (95 % CI 1.041, 2.203) and 1.9 (95 % CI 1.078, 3.495), respectively. An association with other polymorphisms of cytokines *IL-1b*, *IL-1RA*, *IL-10* and *CD14* was not found in the same study (93). The genotypes GG and G of the *IL-6* gene are associated with an increased IL-6 production that could contribute to the development of pro-inflammatory responses in the intestinal mucosa. Finally, an association of MC with HLA DR3-DQ2 haplotype and *TNF2* allele has also been found (94). Further studies are needed in order to strength the knowledge on the role of genetic factors in the origin of MC.

FROM BENCH TO BEDSIDE: TREATMENT OPTIONS FOR MC

The treatment of MC should take into account the severity of symptoms and their impact on the patients' quality of life, the efficacy of the drugs in obtaining clinical remission (accompanied or not with histological remission), and the secondary effects associated to short and long term treatments. Considering the high rate of spontaneous remission and sustained remission after short term therapy, the long-term therapy should be considered preferentially on relapsing or refractory patients, for whom an intermittent therapy should be favored (4). In recent years, a number of randomized controlled trials (RCT) have been provided for a more evidence-based approach to treat MC patients. More evidence is available on the treatment of CC than LC, but there is no reason to treat these two entities differently, because the drugs that seem to be effective in one tend to be effective also in the other disease. Several medical treatments have been studied in MC patients, following empirical approaches. In fact, currently there is no casual treatment approach for MC, although increasing data on the effects of some drugs over pathogenetic mechanisms involved in the development of MC are now available.

Induction of remission and maintenance treatment in patients with active MC

Budesonide

Budesonide is a non-halogenated gluco-corticosteroid with a very high receptor binding affinity and a limited systemic availability, without the significant adverse events that frequently occur in systemic corticosteroids-based treatment. Budesonide is currently the most promising treatment for MC; the strongest evidence on its efficacy, coming from several RCTs. It should be considered the first-line treatment in active MC (4). Three RCT in CC (95-97) and two in LC (98,99) have demonstrated that budesonide therapy (9 mg/day for 6-8 weeks) is effective in inducing the clinical remission and to improve the patients' health-related quality of life. Furthermore, in a recent study, budesonide was significantly superior to mesalazine for inducing clinical remission (80 % *vs*. 44 %, p = 0.0035) in CC patients (100). Two Cochrane Collaboration systematic reviews with meta-analysis reported a high response rate for achieving a clinical remission compared to placebo, with a pooled response rate of 81 % in CC (101) and an odds ratio of 9 in LC (102), with these last results also confirmed by other recent meta-analysis (103). However, a high rate (61-80 %) of relapse within 2 weeks after stopping the treatment was reported in all trials, which required studying the benefit of a maintenance treatment. In fact, two RCTs have shown that clinical remission and histological response can be maintained with budesonide at a dose of 6 mg/day for 6 months (104,105), and a mean dose of 4.5 mg/day maintained clinical remission for at least 1 year in 61.4 % in CC patients *vs*. only 16.7 % in the placebo group ($p < 0.001$), with few adverse drug reactions. As a whole, these results suggest the usefulness of maintenance treatment with a low-dose of budesonide, to prevent this high relapse rate (106).

Regarding the mechanism of action of this drug, we know that the glucocorticoid receptor is ubiquitously found in nearly all tissues and its interaction with the cells and mediators plays a key role in the inflammatory cascade, preventing epithelial dysfunction *in vitro* models of inflammation, by inhibiting the activation of both T-cells and monocytes (107), modulating the inflammatory regulator NF-KB (108) and acting by other different mechanisms (109,110). However, we still lack enough data about what are the exact mechanisms by which budesonide acts in order to produce its therapeutic effect in MC patients. From the few data available, we know that budesonide can modify the different lymphocyte subpopulations infiltrating the intestinal mucosa in MC patients, as showed by immunohistochemical staining and flow cytometric analysis (96,98,111). In fact, budesonide treatment is often associated with the restoration of histology in a majority of LC cases, and with a partial or complete normalization of the inflammatory infiltrate in 30.8 % and 69.2 % CC patients, respectively (112). In contrast, a recent study failed to demonstrate significant reductions in the proportion of total CD8+ intraepithelial T-cells, when T-cells from lamina propria were separately analyzed by flow cytometry in budesonide-treated LC and CC patients (64). In the same study, no differences in the proportion of CD45RO+ or Ki67+ cells, nor CD8+ or CD4+ intrahepitelial and lamina propria T-cells, between untreated and budesonide treated patients with MC were found, except a single LC treated patient showing a declined proportion of these cells. A declined proportion of CD4+8+ lamina propria and IELs cells were only found in CC treated patients, but not in LC patients (64). A reduction in the thickness of the subepithelial collagen band can be seen in treated patients with CC, but it seems to take a longer time than for the resolution of the inflammatory infiltrate (112). Moreover, budesonide treatment can reduce the *iNOS* mRNA expression that correlates with the inflammatory and the clinical activity of CC patients (113). Finally, the efficacy of budesonide in MC might be in part also due to an increase in the ileal reabsorption of bile acids (114). However, there are some pathogenetic mechanisms on which budesonide has no effect, as demonstrated by the persistent mucosal barrier dysfunction after budesonide treatment (51) despite of the fact of restoring the electrogenic sodium transport impairment (115) and the altered mucosal reactivity (51).

Mesalazine

5-Aminosalicylic acid (5-ASA) such as mesalazine has a local anti-inflammatory effect, as demonstrated also in other inflammatory bowel diseases. There are few evidence-based data about its usefulness in MC patients. In retrospective studies 5-ASA have been shown to be effective in about half of the patients at a dose of 2.4-3 g/day, with an effective rate ranging from 86 %-42 % in Spanish studies, to 35-42 % in American and other European studies (116-119). Prospective open-label studies showed one high efficacy of mesalazine for inducing remission in MC (73 % in CC and 85 % in LC), especially when combined with cholestyramine in CC patients (102,120). However, in the unique RCT published, mesalazine resulted less effective than budesonide and placebo to induce clinical remission in CC patients (100). Therefore, the current value of mesalazine for the treatment of MC patients remains unclear and further studies are needed.

Cholestyramine

Even when cholestiramine has never been assayed in a RCT, evidence from uncontrolled retrospective data shows that this bile acid binder (at a dose of 4 g/day) could be effective in MC, especially in CC patients with a concomitant BAM (121). As stated above, the benefit of cholestyramine is slightly better if combined with mesalazine, as showed in a prospective no placebo-controlled study (120); these data need to be confirmed to clarify the real therapeutic value of this drug. In fact, patients on bile acid binders had no significant changes in histopathology, despite a good effect on their symptoms (122). However, it is important to highlight that its beneficial effect is not only bile acid-specific, as cholestyramine also binds bacterial toxins, which might also contribute to reduce the symptoms in MC patients by a bile acids independent mechanism, which highlights the important role for luminal antigens in the pathogenesis of MC.

Other treatment options

Loperamide

Some drugs could be used to produce symptomatic effect such as loperamide, which does not achieve sustained clinical remission and produces no impact on colonic inflammation. However, loperamide could be reserved to control symptoms in mild cases of MC (123).

Probiotics

Probiotics are other treatment whose potential role in the induction and/or maintenance of clinical remission in MC should also be further investigated. Until now, they have been exclusively investigated in CC patients: In particular, *Lactobacillus acidophilus* LA-5, *Bifidobacterium animalis subspp lactis* BB12 and *Boswellia serrata* extracts did not show benefit, in terms of clinical and histological response or in improvement of quality of life, compared to placebo (124,125). Only the probiotic *Escherichia coli* strain Nissle 1917 has achieved in an open-label uncontrolled trial a reduction in stool frequency in 64 % of CC patients (126).

Bismuth derivatives

Bismuth subsalicylate, a derivative of salicylic acid with potential anti-inflammatory and antibacterial actions has occasionally been used in America on mild to moderate active MC: A RCT and an additional open-label study showed clinical and histological response in MC patients (127,128), but toxicity concerns have determined that this drug is not available and not used in many countries.

Therapeutical options for refractory MC patients and future prospects

Only a small subset of patients with MC are refractory to steroids treatment, amounting approximately less than 5 % in a population-based cohort study (129). In patients who failed to respond and in patients intolerant to budesonide, the use of immunosuppressive therapies should be considered, once confirmed the histological diagnosis of MC, carried out a correct differential diagnosis, ascertained the compliance to the treatment prescribed and the absence of exposures to high risk medications for MC. However, the experience with immunomodulators in MC is mainly anecdotal, with no RCT available until now, and with its use mainly derived because of the pathogenetic similarities between MC and inflammatory bowel diseases. In particular, Azathioprine or 6-Mercaptopurine, have been demonstrated useful in some MC patients refractory to budesonide with a response rate of 89 %, associating a steroid sparing effect. However, approximately 50 % of MC patients were intolerant to these drugs (129,131). Doses used in MC have been very similar to that of inflammatory bowel disease. Methotrexate (MTX) has also been studied in a retrospective report on CC patients, showing a beneficial effect with oral low-dose (5-25 mg). However, most patients in this report had not been previously treated with budesonide (132). In contrast, a prospective study conducted on patients intolerant or refractory to budesonide who received subcutaneous MTX (15-25 mg) showed no clinical remission (133).

An effective use of anti-TNF therapy (infliximab and adalimumab) has been reported in refractory severe MC

patients, as a third-line treatment or "rescue therapy" to avoid surgery (diverting ileostomy or colectomy) in selected intractable cases (134,135). On a pathogenetic point of view, the TNF-alpha released by activated macrophages and T-cells triggers a chain of cellular mediators that causes secondary intestinal damage. Limited data have shown an increased expression of TNF-alpha in the colonic mucosa of MC patients (136,137), although at a very weak level (< 10 % in epithelial and inflammatory cells of MC patients) (83). A putative role for IL-17 in the pathogenesis of MC has been recently proposed, after documenting an increased expression in epithelial and inflammatory cells of MC patients (83). In fact, the regulation of IL-17 appears as a viable future therapeutic option in the treatment of MC patients, since a novel inhibitor of the production of IL-17 in activated lymphocytes (Vidofludimus) has been studied in animal models of chronic intestinal inflammation (138). The better understanding of the molecular mechanisms behind the development and maintenance of colonic inflammation in MC patients will make possible the development of future specific drugs to control disease activity. Evidence-based data deserve further prospective studies to obtain more conclusive data regarding this small subset of patients.

CONCLUSIONS

Knowledge about MC has constantly increased since the first description of the disease, to the point that CC and LC have been established as well-defined diseases. MC is currently considered as a worldwide condition, as common as inflammatory bowel disease. However its pathogenesis still remain unknown and the approach to the treatment of MC patients is mainly empirical and not causal, based on very comprehensive evidence. Fundamental advances in the understanding of the pathogenetic mechanisms of the development and maintenance of chronic intestinal inflammation in MC patients are needed, to further allow the development of novel and effective specific therapies.

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