Reviewer's report

Title: Smoking habits in relation to the clinical picture of women with microscopic colitis compared to controls

Version: 2 Date: 30 August 2013

Reviewer: Lars Munck

Reviewer's report:

The study of Roth et al seeks to provide controlled information on the relation between smoking and microscopic colitis. This issue is important and at present not resolved. However, the disproportionate focus on irritable bowel syndrome and alcohol muddles the message. The paper could be very interesting if rewritten with a clear focus on the issue indicated in the title and a more balanced description, analysis and discussion of the other data. A number of methodological issues need clarification.

Scope

It remains unclear why smoking habits are explored in relation to IBS and other life style factors. Likewise, the association with alcohol is introduced without a clear justification. Is the increased wine consumption really an issue in the very elderly, i.e. those patients driving the increasing incidence of MC?

Material

Restricting this to women is acceptable and justified. However, the exclusion of patients aged 73 or older is more problematic, as incidence increases throughout life. The choice should be justified, as concomitant diseases and drug therapy appears less relevant given the newer information, that drugs most probably has no or minor association (Bonderup, DDW and ECCO 2013), and that patients do not have more concomitant diseases than others with the same age. The present population is probably not representative for the MC population and maybe not for their smoking habits.

Patients were interviewed retrospectively, some apparently several years after diagnosis. This would most likely induce a recollection bias. It appears from the legend to figure 4 that the answers relate not to time of diagnosis but to the time of participation in the study. This should be stated clearly in the methodology section. As the answers relate to the time of questionnaire any relation to MC diagnosis and course would appear to be questionable.

It is acceptable to study LC and CC together, and a previous systemic analysis demonstrated identical symptoms and findings in these two groups (Rasmussen et al, 2012).

The control group was younger and without abdominal complaints and thus not an optimal comparator. In particular, one would expect smoking incidence to differ from that of an older population. Why were patients with breast cancer and
not other serious diseases excluded? Many women with MC have or have had breast cancer.

Finally, the statistical analysis excludes patients due to criteria not mentioned in the material section. Was this specified in the study protocol? If not they must stay in the analysis. Despite this selection the groups still differs with regard to age, causing further concern about the selection. Please justify or redo the analysis leaving these patients in.

Diagnosis

Both diarrhoea AND pathological findings are needed for the diagnosis of MC, and stating “symptoms” (introduction line 2) is imprecise. Thus, the diagnosis can not be made on the basis of pathological findings alone, as stated in the introduction. The distinction between MC with a single attack and relapsing MC is highly relevant and not sufficiently studied in general, but stating that at least two episodes are needed for a diagnosis of IBD is not correct, and for MC not validated. It is true that the incidence differs greatly between Sweden and other countries including USA and Denmark (Bonderup, 2013), and this discussion is important but at present not resolved. Two biopsies demonstrating MC were required for the diagnosis, and this strict criterion has not been sufficiently examined nor discussed, and a consensus has not been obtained. It may well be an explanation of the lower Swedish incidence. “Secondary” MC is not a generally accepted term, and MC can coexist with (quiescent) celiac disease.

Parameters

The results of the various questionnaires reflect symptoms at the time of interview which can be many years after the diagnosis. This limitation with regard to the key issue of association with MC must be thoroughly discussed and justified. Symptoms will change over time, and patients with a chronic disease will learn to cope with this and thereby most likely change opinion on several of the questions..

Analysis

An overwhelming number of analyses were performed without correction of the level of significance. The subgroups compared were in many cases small. The exclusion of patients is not acceptable if it is not stated in the study protocol.

Results

These are many, and some could be left out without compromising the main focus. For instance table 3 could be referred to providing data. It remains a puzzle to this assessor, why so many data on drinking are provided. Even more so as there are many missing data. Consider providing only the main data.

Please state clearly at what time in relation to the MC diagnosis the questionnaire data refer.

The last three lines in the result section may not be a true reflection of the results but merely the result of confounding. Perhaps smoking and IBS symptoms are associated? Anyway, since the data are retrospective, any statement of “risk”
should be avoided, because a causative association was not demonstrated.
Only a small part of patients with active MC have an elevated CRP, and CRP is not a trustworthy measure of MC activity.

Discussion
At present, MC is a diagnosis based on diarrhoea + histology, while IBS is based solely on symptoms. The discussion focuses on IBS and functional diseases and often gets out of the (MC) focus. The authors should rewrite this part or change the title.
Since there is no association with alcohol the extensive discussion of the effect of alcohol on mucosa etc. appears somewhat misplaced. Consider to tighten the discussion and to leave out these parts.
There is yet no evidence of an association between gut microbiota and MC at present (page 14, 2. paragraph) and therapeutic trials with probiotics have been negative.
Previous studies have demonstrated a short duration of symptoms prior to the MC diagnosis, at least during the last 10 years. While the notion that MC patients risk being considered to have IBS is partly true, there is significant difference with regard to symptoms. As also stated, patients 50 or older will have an endoscopy with biopsy. This can however not explain the increasing incidence with age, since the median age at diagnosis is 63 years.
The proposal to strengthen the criteria for MC may be relevant, but should be based on relevant data. The data presented in this paper do not support the proposal.
Tables
Table 2 and 3 lack confidence intervals.
In Table 2 it would appear more logical to state the % of MC1 and MC2 respectively with symptoms of IBS. Table 3 lack numbers, but could be left out.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'