

June 9, 2015

Dear Editor,

ESPS Manuscript NO: 18280

Please find enclosed revised manuscript in word format (file name: 18280-edited June.docx). The manuscript has been revised according to the suggestions of reviewer 03317237 and reviewer 03317062.

Response to Reviewer 03317237:

1. I included epidemiological studies to show the incidence of MC in the U.S. and around the world. The incidence of MC in Sweden, Spain, and Iceland from the 1990s ranged from 1.1 to 5.2 per 100,000 person-years [1]. In a population based cohort study conducted from 1985 to 2001 in Olmsted County, Minnesota, the overall age and sex adjusted incidence of CC was 3.1 per 100,000 and that of LC was 5.5 per 100,000 [1]. Poisson regression analysis showed that the incidence of MC increased over time, and the incidence of MC by the end of 2001 was 19.6 per 100,000 [1].
Gut 2007;**56**:504-8. PMID:17135309. doi: 10.1136/gut.2006.105890
2. "And/or" was used per reviewer's suggestion.
3. ">20 intraepithelial lymphocytes per 100 epithelial cells" was corrected per reviewer's suggestion.
4. "Inflammatory infiltration" was replaced with "inflammation in the lamina propria with mainly mononuclear cells" per reviewer's suggestion.
5. References were added to the Figure 1 for diagnostic criteria per reviewer's suggestion.
6. Smoking as risk factor for MC: Study from Sweden was included. *Scand J Gastroenterol.* 2011 Nov;**46**(11):1334-9
7. Drug-induced MC data: I could not identify the specific paper that the reviewer alluded to but I found an excellent (and recent) Dutch study supporting drug exposure (specifically to PPI and NSAIDs) increasing the risk of MC.
8. Studies analyzing immunopathology of MC: I included more data on cytokine profile from Barmeyer's study but this particular study did not comment beyond IFN- γ , TNF- α , IL-1 β , IL-13, and IL-8. I added data from Tagkalidis's study to support similar cytokine profile (elevations in IFN - γ , TNF- α) found in MC patients.
9. Bismuth study: I added the details of the study to clarify that the study was based on mice models for inflammatory bowel disease, not MC.

Response to Reviewer 03317062:

1. Is there a difference in immune response in patients with LC and CC: There is no subgroup analysis for LC and CC patients in Barmeyer's study with cytometric bead arrays for us to comment on significant differences in cytokine profiles between LC and CC patients. Due to insufficient data, we choose not to comment on differences in cytokine profiles in patients with LC and CC.
2. It is difficult to grasp the details of studies on immunomodulators and anti-TNF-a, please show agents, dosage, duration in a Table: Table 3 was created to address this concern.

Other revisions:

1. Font type and size were corrected to Book Antiqua and size 10.
2. Reference was formatted, and both PMID and doi numbers were included for each reference.
3. Abstract was revised to meet the word count criteria(>200 words).
4. Core tip was created (under 100 words).
5. Key words were created.
6. Running title was created.
7. Corresponding author information was included.
8. Conflict of interested was included.
9. Figures and tables were removed from the main body of the manuscript and were attached as a separate word file (file name:Figures and Tables.docx).

Thank you for your feedback and considering our manuscript for publication.

Sincerely,

Tina Park, MD, David Cave, MD, and Christopher Marshall, MD

Gastroenterology

University of Massachusetts

55 Lake Avenue North

Worcester, MA 01655

USA

Tina.Park@umassmemorial.org

David.Cave@umassmemorial.org

Christopher.Marshall@umassmemorial.org