

Format for ANSWERING REVIEWERS



December 21, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5336-REVIEW UK19122013.doc).

Name of journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5336

Columns: META-ANALYSIS

Antiviral therapy in cytomegalovirus-positive ulcerative colitis: a systematic review and meta-analysis.

U. Kopylov, N. Eliakim-Raz, A. Szilagy, EG. Seidman, S. Ben-Horin, LH. Katz.

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated in accordance to the editor's instructions

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1

We agree with the reviewer's assessment of the low quality of the included studies. Indeed, none of the included studies were randomized controlled studies, and those are unlikely to be undertaken in the near future. However, we strived to include only the papers with the most reliable methodology among those available. In the included studies we have described the strategy leading to decision to use or not use antivirals, if such strategy was clearly described. We believe that our manuscript represents a valuable synthesis of the existing literature, despite all of its flaws, and raises important questions for further research. We definitely agree with the reviewer regarding the potential biases (such as the possibility that patients who received antivirals were sicker than those who were not) and had further emphasized and described this and other potential biases in the discussion. We have also stated in the summary that our conclusions should not be interpreted as a recommendation to abstain from antiviral treatment in this entire cohort, but as a suggestion that this cohort is very heterogeneous and includes subgroups of patients that may not require antiviral treatment.

As for the mode of administration of antiviral treatment, a vast majority of the patients included in our study were treated intravenously with variable durations of treatment. This reflects the lack of clear evidence-based guidelines and recommendations specific to IBD patients (the suggested treatment strategy is based on the experience with other categories of immunosuppressed patients), that should definitely be addressed in future studies.

Reviewer 2:

We definitely agree with the drawbacks of the existing literature on the described subject. However, we believe that our work represents the best possible synthesis of this data, as flawed as it is. We have employed a stringent inclusion strategy and have formulated our conclusion very carefully, emphasizing all the potential biases and drawbacks. We believe that our study underscores several important points such as the heterogeneity of the patient cohort and the unclear benefit of the treatment for all patients. Our conclusion does not aspire to claim that antiviral treatment has no value.

but rather to state that patient subgroups benefitting from the treatment, along with the exact indications and protocol, need to be better delineated.

Reviewer 3

In light of the reviewer's valuable comments several changes were undertaken:

1. The limitations and potential biases were significantly enhanced in the discussion and the abstract.
2. All comments appearing in the results section were removed
3. An additional subgroup analysis by country of origin was undertaken as requested. The results did not change on exclusion of studies from Israel and Canada
4. The lack of sufficient mortality data was added as an additional limitation, as requested, and the analysis of mortality rates was excluded from the results and the abstract.
5. The limitations section was enhanced and expanded on expense of the "strengths" section
 - a. 3 References and typesetting were corrected.

Reviewer 4

We would like to thank the reviewers and the editorial team for the positive view of our manuscript. In light of the reviewer's comments, we have added a figure (3) that demonstrates positive HE/IHC staining for CMV, and a flowchart (figure 4) that contains a suggested algorithm for management of histologically CMV-positive patients stratified by initial response to anti-inflammatory treatment

Reviewer 5

We would like to thank the reviewer for the positive opinion regarding our manuscript.

1. We have emphasized the results pertaining to histologically positive patients both in the abstract and the conclusions.
2. The abbreviations were corrected as requested.

Sincerely yours,

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