

ANSWERS TO REVIEWERS

Please find below our answers to the constructive remarks of the 5 reviewers. In this section, the text of the reviewers was copied in *italic characters*. Our answers appear in **bold characters**. In addition, we provide a marked version of the manuscript that **enlightens in yellow** the major changes that were performed in comparison of the initial version of the paper.

1. Reviewer 02441274

Overall an excellent review of association of CMV and IUC. Only suggestion is a professional help to improve grammar and language. While the context is very comprehensive, the English is poor and at places bad. Just for a few examples: 1. None of author's abbreviations is PP. Author contribution in title page needs correction. 2. Abstract line 7- to be reframed as "Although CMV activation can be considered as innocent by stander more and more studies suggests a deleterious role of CMV in this situation....." 3. Introduction 2nd para last line should not end with but with etc. 4. Page 8 1st para 3rd last line should be colonoscopy rather "coloscopy" 5. Page 16 2nd para,3rd line should be "on which antiviral drug should be used and for what duration." 6. Page 16 2nd para, 6th line- should be "In contrast to " rather than " By contrast to." 7. Some of the abbreviations in table are not explained at the end of table such as PBMC and NAAT in Table 1.

The English language was revised extensively thanks to the help of a native-English scientist (see enclosed certificate). All the points specifically stressed by this reviewer were carefully corrected.

2. Reviewer 189171

Pillet et al. highlighted both of our clear knowledge and the dabetaes regarding the cytomegalovirus infection in ulcerative colitis. The authors have their own practical and scientific experiences on this field. This fact has a beneficial effect on this review. The manuscript is well structured and well written, however the conclusions should be more moderate in my opinion.

Thank you for this positive opinion. As recommended, the conclusion was rendered more moderate (see § Concluding remarks, page 20 of the new version).

I have some other remarks as the followings: Sensitivity and specificity of each diagnostic method should be accurately signed in the text. Without these data the reader will not be able to judge the real diagnostic accuracy of the mentioned methods. These data are lacking from the section discussing the predictive factors of unfavorable evolution of UC (page 13).

Because of the diversity of the tests used in the different studies listed in this review, it is very difficult to assign a precise specificity for each of the techniques that were mentioned. The absence of technical standardization explains in great part the differences of appreciation discussed in this review.

Author states that NAAT test do not have any information regarding the infectious potential of the detected CMV infection, compared to IHC. Based on this, it seems that IHC has a very significant advantage compared to NAAT methods. If it has any impact to the decision making in the daily clinical practice, authors should emphasize this difference.

IHC as well as NAATs need the use of thresholds in order to define which samples must be considered as positive. A great part of the section dedicated to the techniques (pages 7 to 9 of the new version) deals with the definition of these thresholds, notably for NAATS. A sentence has been added at the end of this section (last sentence in the second § of page 9 in the new version) to reinforce this point.

Time frames between biopsy taking and results of each test should be discussed in my opinion. In a case of a severe colitis this time-frame may have a high importance. I would read something about the authors' opinion regarding the optimal sites of biopsy taking. They offer to perform a multiply biopsy, however there is no advice regarding the place. Should we take samples from the most severe ulcers (even deep ones) or from the places with confluating erosions? Is it useful to take biopsy from the unaffected parts situated near to the border of inflammation?

A sentence has been added regarding the interest of performing biopsies from places exhibiting ulcers (last sentence of page 8 in the new version). The importance of ulcerative lesions is also discussed with the factors of severity (page 15, second § of the new version).

Age under 30 is referred as an independent risk factor for CMV reactivation in UC patients. The evidences regarding this factor seems less robust for me compared to other mentioned factors (2 studies, more less patients, more heterogeneous patient population, more week statistics). Authors should discuss this fact, in my opinion – conclusion regarding this statement should be more shaded.

A sentence at this end of this section (page 12, second § of the new version) has been added to moderate this criterion and to ask for additional studies in order to confirm this finding. However, the two studies reporting this association are very recent and exhibit a strong methodology (refs 41 and 84). It is also our personal experience.

I willingly read a less definite and a longer conclusion section at the end of the manuscript. As author have clinical and research experience on this field, they are able to summarize the “take home message” more discreet.

As mentioned above, the concluding remarks (page 20 of the new version) have been written in a more moderate way: “Despite conflicting results, there is increasing evidence, notably in recent studies, ...”; “...appears to be highly recommendable...”.

Formal and writing remarks: As IFN is not a cellular factor of the immune system, the first sentence of the 2nd paragraph of the introduction section should be reworded in my opinion.

This sentence was amended according to the relevant remark of the reviewer (page 5, second § of the new version).

The “...” on the end of the same paragraph is very unusual, it could be replaced by with a more conventional “etc”, for example.

The correction was done accordingly.

Figure 1 – is the picture as are originated from the own works of the authors, it is Ok, otherwise the origin of them should be signed due to copyright issue.

Permission was asked for reproducing pictures that are not from our works.

I’m not sure that the form of the listing in the section regarding the implicated factors (starts on page No. 10) are fits for the journal formal requirements. In any event, it differs from the style of the listing performed in the paragraph about the predictive factors.

It is not clear for us why this section does not fit the requirements of the WJG.

Unit of leukocyte number is not the conventional one in the paragraph regarding the other predictive factors (page 12). Moreover, high leukocyte count might be the consequence of the corticosteroid therapy....

The unit for leukocyte number has been changed (< 11,000/ml) (page 13, line 7, in the new version).

Form of the signing of odds ratio is not the conventional one I suggest to use the “OR:4.7; CI(95%): 1.2-22.5” form. With this change, the important odds ratio is clearer for a clinician.

The form for odds ratios was modified accordingly to the remark of the reviewer all over the new version of the manuscript.

Authors use the term “pejorative” in some places of the manuscript. Subjectively, I would prefer the term “unfavourable” or other terms instead of it.

We agree that the term “unfavorable” is more suitable than “pejorative”. The change was done accordingly.

I’m not sure that a citation as long as it is cited in the page 16 is a very lucky form.

Despite the fact that this citation is long, it seems important for us to cite it extensively because it is a strong recommendation from a reputed Society. It reflects the present state of the art in this matter.

In summary, this is an important review from the viewpoint of a clinician, helping to understand the pitfalls of the diagnostic workup regarding CMV infection in UC. There are some missing data (sensitivity and specificity, etc.) and some formal remarks.

We thank again this reviewer for his/her very careful reading of our manuscript. These constructive remarks were of great help for improving the quality of our manuscript.

3. Reviewer 1429143

This is well-done, comprehensive and update review.

Many thanks for this encouraging comment.

I have only minor remarks/suggestions: a) The English style needs revision

As stated above, the English language was carefully revised (all the changes are highlighted in yellow in the marked version of the new manuscript).

b) Please comment more in the text regarding the usefulness (if any) of antigenemia (cut off ?) and fecal PCR.

To our knowledge, no threshold of pp65 antigenemia has been established for starting a therapy (this point was mentioned in page 10, lines 12-13 of the 2nd §). In our opinion, this test is not adequate for starting an antiviral therapy. With regard to fecal PCR, a sentence was added to mention this technique and its limits in terms of sensitivity (see top of page 9 in the new version).

c) Please comment in the text how to manage the IBD therapy during antiviral therapy?

In answer to this remark, a sentence has been added at the end of the § entitled “Discussion of therapeutic algorithms” in page 20.

4. Reviewer 504725

A comprehensive piece of work. However, the misuse of words and the clumsy sentence structure in many places make the manuscript difficult to follow . For example, the word pejorative is used incorrectly several times. This term is generally used in a disapproving manner to refer to an individual, and is not used appropriately in this manuscript. I do think this is a good paper and if rewritten should be published.

Many thanks for this nice comment. We hope that the improvement of the English style will help to make the manuscript clearer to read. As stated above, the term “pejorative” was replaced by “unfavorable”.

5. Reviewer 68528

Manuscript NO: 22624 Title: Cytomegalovirus and ulcerative colitis: place of antiviral therapy. In this interesting paper, the authors provide reliable and very interesting data on the CMV infection in UC. The article is well written and describes the best and most modern tools for detecting CMV infection and the role of CMV in refractory UC. The Authors focuses on the major clinical aspects of the CMV infection the related clinical complication. I consider this paper suitable for publication on WJG.

We acknowledge the reviewer for this overall appreciation.