

## **Answering reviewer 1**

**Reviewer's comments:** The topic of the manuscript is very relevant. The authors reviewed current studies using CAP in patients with UC showing poor response or secondary loss of response (LOR) to biologics and concluded that combination therapy with CAP could be an alternative therapeutic strategy for biologic-refractory ulcerative colitis. Despite a generally well-prepared manuscript, the statistical analysis of data from several heterogeneous studies cannot be qualified as acceptable. First of all, we can note the incorrect calculation of the average remission rates. In the submitted form, the manuscript cannot be published. It is recommended to use a more correct statistical analysis or meta-analysis. The manuscript can be recommended for publication only after revision.

**Answering the comments:** Thank you very much for reviewing our manuscript and giving us very valuable comments and suggestions. We have revised the manuscript according to your comments as follows. We would appreciate it very much if you could review the revised manuscript.

As the reviewer pointed out, heterogeneity existed especially in the efficacy of the combination therapies with CAP and biologics. In the revised manuscript, we have evaluated the efficacy of the combination therapy with CAP and biologics as well as CAP therapy in a more appropriate way as follows. Although number of the samples was small, we have shown the rates of remission/response and steroid-free remission in CAP therapy and the combination therapies using box plot, and have shown median value, interquartile range, and standard deviation (SD) of them in addition to mean value in the text and Figures in the revised manuscript.

Regarding the existence of heterogeneity among the studies, we have stated this in the section of abstract (Although heterogeneity existed in the efficacy of the combination therapy with CAP and biologics, ...), in the section of Efficacy of the combination therapy with CAP and biologics (As shown in Table 3, there were differences in the background of the patients and methods of combination therapies among the studies, and heterogeneity existed in the efficacy of the combination therapies with CAP and biologics among the studies.), and in conclusion (Although there was heterogeneity in the efficacy of the combination therapy with CAP and biologics in patients with IBD refractory to biologics, ...) in the revised manuscript. In addition, we have added a sentence “In Table 3, it seems that the studies using a higher frequency of biweekly CAP or intensive CAP tended to demonstrate good clinical efficacy.” at the end of the section of Efficacy of the combination therapy with CAP and biologics.

## **Answering reviewer 2**

**Reviewer's comments.** Well-written and referenced, however, it wasn't mentioned how the literature search was done and the timeline of studies that were included in the review.

**Answering the comments:** Thank you very much for reviewing our manuscript and giving us very valuable comments. We have revised the manuscript according to your comments as follows. We would appreciate it very much if you could review the revised manuscript.

In the revised manuscript, we have added the literature search strategy and study selection procedures that include the timeline of studies.

### **Answering reviewer 3**

**Reviewer's comments:** The authors systematically summarize the current literature on the use of CAP for UC patients showing insufficient response or LOR to biologics. Their results suggest that CAP has potential for UC refractory to biologics. However, the quality of this manuscript needs further improvement. 1. The English writing needs to be improved. 2. The current review should briefly describe the literature search strategy and study selection procedures. 3. Throughout this review, event rates of each of the included studies were summarised to derive a range of corresponding rates, but the heterogeneity within studies was ignored, and the presence of heterogeneity makes this simple combination of rates potentially unscientific.

**Answering the comments:** Thank you very much for reviewing our manuscript and giving us very valuable comments. We have revised the manuscript according to your comments as follows. We would appreciate it very much if you could review the revised manuscript.

1. We have performed further language polishing again by sending our revised manuscript to a professional English language editing company.
2. We have described the literature search strategy and study selection procedures in the revised manuscript.
3. As the reviewer pointed out, heterogeneity existed especially in the efficacy of the combination therapies with CAP and biologics. In the revised manuscript, we have evaluated the efficacy of the combination therapy with CAP and biologics as well as CAP therapy in a more appropriate way as follows. Although number of the samples was small, we have shown the rates of remission/response and steroid-free remission in CAP therapy and the combination therapies using box plot, and have

shown median value, interquartile range, and standard deviation (SD) of them in addition to mean value in the text and Figures in the revised manuscript.

Regarding the existence of heterogeneity among the studies, we have stated this in the section of abstract (Although heterogeneity existed in the efficacy of the combination therapy with CAP and biologics, ...), in the section of Efficacy of the combination therapy with CAP and biologics (As shown in Table 3, there were differences in the background of the patients and methods of combination therapies among the studies, and heterogeneity existed in the efficacy of the combination therapies with CAP and biologics among the studies.), and in conclusion (Although there was heterogeneity in the efficacy of the combination therapy with CAP and biologics in patients with IBD refractory to biologics, ...) in the revised manuscript. In addition, we have added a sentence “In Table 3, it seems that the studies using a higher frequency of biweekly CAP or intensive CAP tended to demonstrate good clinical efficacy.” at the end of the section of Efficacy of the combination therapy with CAP and biologics.

#### **Answering reviewer 4**

**Reviewer's comments:** Even if the topic is interest, it is not clear which is the purpose of the review and which is the novelty that provides.

**Answering the comments:** Thank you very much for reviewing our manuscript and giving us very valuable comments. We have revised the manuscript according your comments as follows. We would appreciate it very much if you could review the revised manuscript.

According to the reviewer's comments, we have clearly demonstrated the purpose of the review in abstract (This article aimed to summarize the current literature on the use of cytopheresis (CAP) in patients with UC showing a poor response or LOR to biologics and discuss its advantages and limitations.) and in the sections of Introduction (The purpose of this article is to summarize the current literature on the use of CAP as an alternative therapeutic strategy for patients with UC showing insufficient response or LOR to biologics and discuss the advantages and limitations of this strategy.).

In the revised manuscript, we have added a sentence (As described above, recent studies have shown the efficacy of use of CAP in UC patients showing a poor response or LOR to biologics, but the results of these studies have not been summarized to date.) in the section of Introduction in addition to the sentence (We first summarized the efficacy of CAP for such patients.) in Core tips. We believe that novelty of this manuscript is that we first summarized the efficacy of CAP in UC patients showing a poor response or LOR to biologics. In this context, we have especially emphasized the efficacy of the combination therapies with CAP and biologics in patients with UC refractory to biologics.

In addition, we have performed further language polishing again by sending our revised manuscript to a professional English language editing company.