

REBUTTAL LETTER

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors:

1. Very well written, it would be great if the article could be a systematic review. We greatly appreciate the reviewer's positive comment and agree that a systematic review / meta-analysis would have been better. In fact, we initially considered it that way, however we found that for most of the drugs analyzed, with the exception of corticosteroids and Tocilizumab, there were hardly any prospective and randomized quality studies. In most cases these are retrospective and observational studies, so it did not make much sense to carry out a systematic analysis and we decided to carry out a narrative analysis.

2. Kindly see if the number of references could be decreased or not.

We have eliminated some fragments of the manuscript (based on your observation n° 8), so consequently we have also reduced the number of references compared to the original version.

3. Please provide a chart/figure for the systemic review, accordingly modify the methods section and explain in short the exclusion and inclusion criteria. The idea of a flowchart is good and would be very useful in the case of a systematic review. Unfortunately, as this is a narrative review, it is not possible to perform the figure due to the heterogeneity of the articles analyzed and the variety of treatments reviewed (12 different drug families) –

4. For table 3 heading the word "patients" It would be better to specifically mention if these are Covid-19 patients.

We agree. We have modified it as the reviewer indicates.

5. In some sentence like reference 60 it was mentioned that mortality decreased it would be better to mention if the difference is significant or not.

We agree in that point, and It has been adequately indicated.

6. If possible add additional chart summarizing the adverse events seen in the patients treated by various drugs mentioned in this article.

In the last column of Tables 2 and 4, the infectious complications associated with the treatment with anti-IL-6 and with corticosteroids in the different studies have been collected. Superinfections and opportunistic infections are, by far, the most frequently

described side effect in the literature associated with immunosuppressive treatment. Making a table with other side effects and in relation to the rest of the drugs (used much less frequently) would, in our opinion, be the object of another study and would greatly lengthen the present work.

7. Covid-19 pneumonia is largely associated with fungal pneumonia the drugs used to treat it was not discussed at all.

We consider CAPA (COVID associated pulmonary aspergillosis) to be an infectious complication associated with COVID-19. Whether it is associated with immunosuppressive treatment or with the pathogenesis of the virus itself (as occurs with IAPA in influenza) is currently the subject of debate and we consider that it is beyond the scope of our study.

8. Whereas search was not performed for ECMO or use of convalescent plasma therapy but were discussed in the body.

The reviewer is right. We have added convalescent plasma therapy as another search criteria. ECMO is not mentioned in the present work as an immunomodulatory therapy. We believe that the reviewer refers to the comment on the use of adsorptive cytokine filters (which in some works are used in critical COVID-19 patients who also require ECMO therapy)

9. I feel better to stick with the story of drugs, even bronchoscope were used for therapeutic purposes in critically ill Covid patients.

Bronchoscopy does not have an immunomodulatory effect, unlike adsorptive cytokine filters. However, we have respected the reviewer's criteria and eliminated the section on this type of therapy from our review, since it is not actually a drug but a device.

Science editor:

The manuscript elaborated a review of immunomodulatory therapy for the management of critically ill patients with COVID-19. I find it a well-structured interesting study. Nevertheless, there are a number of points that may deserve some revisions.

1. Although the author has collected detailed literature, too complicated content is not suitable for the author to read.

We have tried to simplify the content

2. The author table should use a three line table, and the font should be uniform.

The tables have been modified according to the editor's instructions

3. The part of SARS-CoV-2 pathogenesis, immune response, and inflammation should simplify.

That part has been simplified and shortened as suggested by the editor.

Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Critical Care Medicine, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

The tables have been modified according to the editor in chief instructions