

## Author Response

### Reviewer 1

1. Was there a special reason the inclusion criteria for age was 19 years?

ANSWER: As this article is a literature review, we used some filters to narrow the results. Since we wanted to do the review on adult population, we chose to filter by age, which considers adults to be 19 years or older in different databases (18-year-old patients are considered to be in the adolescent age range).

2. Biologics are very expensive in contrast to steroids and itraconazole. This should be mentioned in the discussion. Furthermore, they are off label in the therapy of ABPA in most/all countries worldwide.

ANSWER: We completely agree it is important to mention this aspect, so we added to the discussion that biologics are far more expensive than standard of care and that authorities have not endorsed their use for management of ABPA (therefore they are an off-label therapy).

3. If you take the ISHAM Criteria where  $igE > 1000$  is mandatory for ABPA diagnosis, some of the study patients would have to be excluded. You can avoid this taking the Rosenberg Patterson Criteria.

ANSWER: We added to the introduction section (as well as in table 1) the Rosenberg and Patterson diagnostic criteria, explaining both criteria could be used.

4. Table 1-5 exist in 2 different versions. Probably you just have to change the numbers 7-12.

ANSWER: This article only includes 6 tables: table 1a and 1b corresponds to diagnostic criteria for ABPA, Tables 2-6 correspond to the study results, where there is a table for each biologic (except for Omalizumab, which has two tables, one for asthmatic population and the other for patients with cystic fibrosis).

### Reviewer 2

1. The formatting of the manuscript requires attention. The use of multiple subheading within results is confusing and difficult to follow.

ANSWER: We tried to divide the results sections not only in the different biologics but also in the variables of interest. However, we can see how this may be confusing and heavy for readers, therefore we eliminated subheadings in the results section.

2. It is unclear if the authors contacted the authors of previous publications to obtain further clarification of study results.

ANSWER: We did not contact the authors for further clarification of study results. However, we did look at supplementary appendices when provided by the study authors to clarify and complement the results. We added to the methods section an explanation on this matter.

3. The authors have included all the information from table one in the text, I suggest that this is cut down and the table is retained.

ANSWER: We agree this information is not necessary in the text as it is better understood in a table format. We, therefore, eliminated the diagnostic criteria of ABPA from the introduction table and indicated readers to look at table 1.

4. The five stages of ABPA would be clearer in a table format. Were these stages used as descriptors in any of the studies included in the manuscript?

ANSWER: Although we agree tables are easier to understand, we don't believe this classification is extremely important and in fact, it is not widely used in the literature. Therefore, we decided it was not necessary to construct a table with the five stages of ABPA. However, we did not eliminate the stages from the manuscript, since this is a literature review and we must provide detailed information on the disease. Also, we believe that understanding these stages would emphasize on the importance of initiating timely and efficacious management of ABPA, to prevent progression to advanced and irreversible stages.

5. It is surprising that the authors did not mention the association of fungal infection with long term use of corticosteroids.

ANSWER: On the discussion section we further explained that chronic use of systemic steroids lead to systemic effects and increases risk of opportunistic infections, particularly fungal infections.

6. The introduction of the monoclonal antibody treatments is poor, and more information is required

ANSWER: We complemented the information on monoclonal antibody treatments in the introduction section, stating their approved use by the FDA, and their proposed mechanism of action in ABPA.

7. In the methods the authors state that conference abstracts were included and excluded

ANSWER: We planned to include conference abstract when they provided sufficient information. However, only one was included because the others were very nonspecific. This was clarified in the methods section.

8. There is no referencing in the results section. Appropriate referencing needs to be added particularly when referring to specific studies. Mention of specific studies throughout the manuscript does not follow referencing convention.

ANSWER: We made corrections to the references throughout the manuscript. When referring to specific studies we added the reference according to referencing conventions.

9. Patient demographics across all drug groups would be more useful if considered together before digging into the outcome results. This would make it much easier to consider the merits and pitfalls of the reported studies.

ANSWER: We completely agree with this recommendation, so we added a paragraph to the results section, summarizing demographic information and the most important baseline variables across all studies.

10. Throughout the results it is not always clear which studies are being discussed and how many patients are included, therefore when the authors talk about the number of patients it is difficult to interpret if the results reported are meaningful. Inclusion of total numbers being discussed or reporting as % would be helpful.

ANSWER: We understand how the results section might have been confusing. We therefore clarified for each variable, how many studies, including how many patients, reported such outcome. We also added percentages so it is easier for the reader to analyze the results.

11. The results reported in the study lack meaning as no consensus results or statistics have been performed. This is particularly frustrating as there is no referencing to go back and check the original studies in each section.

ANSWER: We decided not to perform further statistical analysis on our study, other than descriptive statistics, because we felt the original studies were very much heterogeneous among them. However, as we said in the recommendations above, we added percentages of patients and referenced the studies included for each variable to make the results clearer for the readers.

12. The authors appeared to have done no detailed analysis of the data collected.

ANSWER: Other than descriptive statistics and a narrative analysis of the results, which was improved after receiving the reviewers kind comments, we felt it was inappropriate to perform further statistical analysis to our results. In this review, we included very few randomized clinical trials, and mostly case reports, case series, and conference abstracts, which have substantial heterogeneity among them. Therefore, we considered further analysis would have given biased results.

However, we do expose the limitations of this review at the end of the discussion section.

13. The first 3 paragraphs of the discussion belong in the introduction.

ANSWER: We reorganized the first three paragraphs of the discussion and moved some of the information to the introduction section, mainly to complement the introduction on monoclonal antibody treatment, as recommended by the reviewer.

14. The discussion lacks structure which makes it very difficult to follow. It is not always clear what biologic or outcome is being reported.

ANSWER: Structure of the discussion section was improved, arranging references for individual studies and specific outcomes.

15. The authors state that all studies reported a significant change in lung function after treatment but no stats were performed to back this up. It is also not mentioned that the change was positive.

ANSWER: Being this a literature review, including several types of studies, we considered it was inappropriate to perform further statistical analysis, other than descriptive statistics. We described with % the amount of patients who had an improvement of more than 10% in FEV1 values, which is a significant clinical cutoff point, as stated in clinical guidelines.

16. There are a number of errors in the English in the manuscript.

ANSWER: The entire manuscript was checked for grammatical and syntax errors.

Thank you very much for your comments on our manuscript,

We will attend future recommendations if needed.