Author's response to reviews

Title: Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: A meta-analysis of randomized controlled trials

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Author's response to reviews: see over
Dear Dr. Nazareno and Prof. Raytos,

Thank you very much for your letter and advice. We have revised the manuscript (MS: 2766961501160593) very thoroughly according to your advice and reviewers’ comments, which you can find our endeavor in the revised manuscript. And we would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the manuscript has been revised. Point-by-point responses to the reviewers’ comments are listed below.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

Look forward to hearing good news from you soon.

With best wishes,

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Point-by-point responses

We would like to express our sincere thanks to the editor and the reviewers for the constructive and positive comments.

Replies to René Jonkers

1. My main comment relates to the apparent lack of novelty of the data presented. Quite recently 2 systematic reviews and meta-analyses were published, one on the effects of macrolide antibiotics in children and adults with non-CF bronchiectasis (Gao et al., PlosOne March 6, 2014) and one on studies in adult patients only (“Shi et al, Pulm Pharmacol Ther, ePub September 2013). The latter publication could at least have been referred to by the authors of the manuscript under consideration, which they apparently choose not to do. The authors have included 3 small studies in their analysis, which were discarded by Gao et al. and Shi et al., being of too low quality. Do the authors have arguments to include these studies? Anyway, the analysis of the authors does not lead to different new viewpoints on the issue.

Answer: We appreciate your comments. When we finished our manuscript initially, we had not found any similar paper published. The topic is so hot that so many people are interested in it. The meta-analysis performed by Shi et al. showed that the number of patients who had at least one exacerbation was significantly greater in the macrolide treated
group. However, the incorrect extraction of data affected the overall accuracy and validity of this meta-analysis, which was also pointed out by Serisier and Gao (PMID:24412272, 24397907). Discussion of it has been made in the revised manuscript (Page 14 line 17-22).

In our meta-analysis, a study was considered eligible if (1) it was a clinical randomized controlled trial (RCT); (2) it assessed the efficacy or safety of macrolides in comparison with placebo, another class of antibiotic or blank control in the treatment of patients with non-CF bronchiectasis. Compared with the meta-analysis performed by Shi et al and Gao et al, our study only individually included one trial made by Yalcin E et al (Journal of Clinical Pharmacy and Therapeutics 2006, 31, 49–55). It was a randomized controlled trial of seventeen patients receiving claritromycin and supportive therapies for 3 months and 17 patients in the control group given supportive therapies only. The outcomes included pulmonary function, sputum production and microbiological findings. This study totally met the inclusion criterion made in our meta-analysis. Owing to the insufficient of large well designed trials, although the quality of study made by Yalcin E et al was not as high as BLESS randomized controlled trial, we had no reliable reason to exclude it. What's more, meta-analysis is a statistical method by summarizing the results of independent studies trials to expand sample size to provide more precise estimates of the effects of healthcare (Oxma
Considering the timeliness of meta-analysis, we prudently searched the databases again. Three additional studies were added to the meta-analysis. One paper was in pediatric bronchiectasis (Valery P, et al, Lancet Respir Med 2013), which we had just searched the study protocol of it in July 2013 (PMID: 22891748). One paper was performed by Cymbala et al, which was excluded due to the full text was not available at that time. Another paper was made by Liu et al, which was omitted in our previous study owing to the lack of data as other trials at that time. We re-extracted data from included studies. We not only analyzed acute pulmonary exacerbations as a function of person-years in patients receiving macrolides compared to control (Figure 2) but also evaluated number of patients stratifying by different exacerbations (Table 1). By subgroup meta-analysis, we could see that the number of participants free from exacerbation was significantly greater and had at least 3 exacerbations was significantly less in macrolide-treated group compared with control group. However, there was no statistical significance of the number of participants had one and two exacerbations between the two groups.

The emergence of new pathogens or increased antimicrobial resistance was a critical issue limiting the widespread use of macrolides treatment. To our knowledge, none of the meta-analysis evaluating this important issue until now. Although trials reported this issue was rare, we tried to
gain some evidence to this important issue. By meta-analysis, we found that eradication of pathogens was improved in the macrolide group (OR=1.55, 95% CI: 1.08, 2.22, P=0.02), while pathogen resistance caused by macrolides dramatically increased (OR=16.83, 95% CI: 7.26, 38.99, P<0.001). The new appearance of a microbiologic profile showed no significant differences between the two groups. More details could be found in figure 5, table 4, additional file 6 and additional file 7. We tried our best to evaluate the clinical benefits and safety of the long-term use of macrolides in patients with non-cystic fibrosis (non-CF) bronchiectasis more comprehensively and more prudently. And we hope our study will bring some objective evidence to clinical practice.

2. The methodology applied by the authors to retrieve the data from the available literature as well as the statistical analyses appear sound. The selection criteria applied to include or discard studies, however, may be questioned as stated above.

Answer: Thank you for your comments. We did this meta-analysis according to Cochrane handbook rigorously. As for the selection criteria, we answered as above.

3. The use of English is generally of poor quality throughout the manuscript. In case it is found worthy of publication I would advise the
authors to ask a native English speaking scientist to correct or rewrite the manuscript. Appropriate reference should be made to the background literature. E.g. background, 3rd para, “Macrolide antibiotics have been effectively used in the treatment of diffuse panbronchiolitis and to prevent exacerbations of asthma, COPD and cystic fibrosis”.

Answer: Thank you for your constructive suggestions. The revised manuscript has been carefully proofread by Dr. Stefan Ryter from Brigham and Women’s Hospital, Harvard Medical School. What’s more, appropriate reference has been added to the background literature.

4. The conclusion of this paper that it presents the first meta-analysis on this subject is evidently not justified. Of at least one of the previous manuscripts, and the most relevant one since it also focuses on adult patients, they could have known since it was published as an ePpub about 6 months ago.

Answer: Thank you for your comments. In fact, we conceived the idea as early as 03 May 2013 (the time we registered at PROSPERO 2013: CRD42013004656). When we finished our manuscript initially, there was no relevant paper published. The topic is so hot that so many people are interested in it. Now it was not the first meta-analysis on this subject. However, we have replenished all the up-to-date studies in the revised manuscript. Three additional paper were added to the meta-analysis.
**Replies to Zhijun Jie**

1. The methods and results the authors used for meta-analysis are right. And overall the discussion is well developed. The only limitation is that the sizes of these 7 studies are small. The authors also need to make this section more clear, focus on the results from the meta-analysis.

   **Answer:** We appreciate your comments. We performed the meta-analysis based on the search from Pubmed, Embase, Web of Science and the Cochrane Library. There were only 7 studies met the inclusion criteria at that time. Considering the timeliness of meta-analysis, we prudently searched the databases again. Three additional studies were added to the meta-analysis. One paper was in pediatric bronchiectasis (Valery P, et al, Lancet Respir Med 2013), which we had just searched the study protocol of it in July 2013 (PMID:22891748). One paper was performed by cymbala et al, which was excluded due to the full text was not available at that time. Another paper was made by Liu et al, which was omitted in our previous study owing to the lack of data as other trials at that time. Now ten trials were included in the meta-analysis. We re-extracted data from included studied. Discussion was more focus on the results from the meta-analysis in the revised manuscript.

2. The statement in the conclusion that "We recommend that patients who
have had more than 2 exacerbations in the past year should be prescribed long-term macrolides therapy", which give clinicians an explicit instruction from this meta-analysis. However, it’s better to insert some caveats to the statement. While there is evidence-based data showed that macrolides do offer benefit in patients with bronchiectasis, there are several other factors that need to be considered when making a decision. These include baseline EKG findings, cardiac risk factors, suspicion for NTM infection, among others.

Answer: We appreciate your suggestion and totally agree with you. The conclusion of ‘We recommend that patients who have had more than two exacerbations in the past year should be prescribed long-term macrolides therapy’ was too bold and lack of consideration. This meta-analysis suggested that patients with frequent exacerbations are prone to be considered to be prescribed long-term macrolide therapy. However, they should be carefully evaluated during the follow up treatment, such as EKG findings, cardiac risk factors and suspicion for NTM infection. Changes have been made in the revised manuscript.

3. Quality of written English: Needs some language corrections before being published.

Answer: We appreciate that you pointed out this problem. The revised manuscript has been carefully proofread by us and a native English
speaker with relevant medicine background.