Author’s response to reviews

Title: Disease severity, debridement approach and timing of drug modify outcomes of adjunctive Azithromycin in non-surgical management of chronic periodontitis: a multivariate meta-analysis

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Author's response to reviews:

Dear Editor

BMC Oral Health

The authors thank the Reviewers for their pertinent suggestions. We have performed a re-analysis of the data keeping in mind these, revised the paper extensively and shortened its length. The main aspect of this revision and meta-analysis is the addressal of some of the key limitations of the previous 2 meta-analyses on this subject. As periodontal pocket depth and clinical attachment loss are variably correlated, a ‘multiple-outcomes meta-analysis of treatments for periodontal disease’ that has been demonstrated previously by Berkey et al (1995), in the Journal of Dental Research was adopted. This approach allowed joint synthesis of correlated outcomes in a single analysis. Furthermore, we also included the 3 moderators in this synthesis and a study-level random variance component. The findings shed light on the sources that may impact the treatment response to adjunctive Azithromycin in non-surgical therapy and raise important points for examination in future studies.

We hope that these insights will drive future research towards better patient selection considering the risks of antimicrobial therapy. The repetition of past findings and knowledge has been
avoided as suggested. In addition, the use of this multivariate approach may be used as an example to similarly jointly synthesise primary periodontal outcomes in future meta-analysis of interventions.

We await further comments in response to these Revisions.

The detailed responses are provided as follows

Reviewer reports:

Müge Lütfioglu (Reviewer 1): The topic of the review is a novel and meaningful about adjunctive usage of antibiotics (esp azithromycin) in peridoontal therapy. There are some statements about the structure of the text that should be corrected by the authors.

1. There are some confusing states about abbreviations. The abbreviations should be written out completely in the text when first used. And also scaling and root planning/ non-surgical periodontal therapy /quadrant wise regime....????There were mistakes that cause misunderstandings about the use of those abbreviations. Those about the situation, abbreviations were highlighted in the text and notes were also attached to the text.

RESPONSE: All abbreviations are corrected.

2. The conclusion sentence in the abstract should be re-written according to this reviewer because of its incoherency.

RESPONSE: The conclusion and abstract are re-written

Peter Bottenberg, PhD (Reviewer 2): The manuscript reports a systematic review and meta-analysis of adjunctive use of azithromycin to periodontal treatment.

This is the 4th in a series of reviews in a rather short period, two published in 2015, the last in 2016. Although in themselves heterogenous (some reporting too elevated bias to perform meta-analysis, some did), their conclusions remain consistent: azithromycin yields a small but
significant advantage. This is fairly well accepted that antibiotherapy in conjunction with debridement can be advantageous.

The four analyses deal with the a selection of 20 articles, citing each between 9 and 15. Concordance between citations is between 47% and 78%. The results of the Forest plot given by Zhang et al (2015) look quite similar to the one in the manuscript (which is of inferior graphical quality).

In my humble opinion, the authors should rewrite the paper from bottom to top. In stead of lengthy disgressions about the use of azithromycin and its benefits (for which referring to existing reviews seems sufficient), they should first make much more clear in what their review is new compared to previous ones and in the discussion focus more on methodological issues like heterogeneity and bias in selecting clinical trials and formulate clear-cut desiderata for further clinical studies. This versus the feasibility of recruiting sufficiently homogenous patients. Then, although the effects were statistically significant, they seem rather small to me. The advantages of azithromycin above control are for me situated very close to the measurement error of the clinical evaluation methods used (ever measured a 0.1mm pocket depth with a probe scaled to 1-2 mm?). Would the effect be significant for patients in saving them pain, discomfort and tooth loss? Is the effect stable over time or should regular administration of azithromycin be considered?

So: shorten considerably the intro and discussion, focus meta-analysis on relevant features compared to the 3 previous reviews, evaluate differences to previous reviews with reference to methodology and selection criteria, give clear guidelines what should be done in clinical studies to improve reporting. Discuss the relevance for patients and public health of antibiotic adjuvants.

RESPONSE: We have performed a re-analysis of the data keeping in mind these, revised the paper extensively and shortened its length. The analysis and discussion is targeted to address key limitations of the previous 2 meta-analyses on this subject. As periodontal pocket depth and clinical attachment loss are variably correlated in different studies, 'a multiple-outcomes meta-analysis of treatments for periodontal disease' that has been demonstrated previously by Berkey et al, in the Journal of Dental Research. This approach was adopted for the current problem. This allowed joint synthesis of CAL and PPD as correlated outcomes in a single analysis and reduces some of the biases inherent in univariate analysis by modelling their within-study covariances. We have also incorporated a between-study (9 studies) random variance component in synthesis of the 11 observations. Furthermore, we also included the 3 moderators examined the study and compared the with moderators and without moderator models. The tables 2 and 3 are updated. The findings add new perspectives and point to factors that may impact the treatment response to
adjunctive Azithromycin in non-surgical therapy and raise important points for examination in future studies.

All the new analysis are performed with the R package ‘metafor’ for multivariate meta-analysis.

We hope that these insights will drive future research towards better patient selection considering the risks of antimicrobial therapy. The repetition of past findings and knowledge has been avoided as suggested. We also hope this multivariate approach may be adopted more commonly to model correlated periodontal outcomes.

Further details: Martan de et al is 2016 (typo in table 2)
Fonseca is referenced as a and b, but only one reference appears.
Table 3: units are missing, we can presume it's mm for CAL and % for BOP.
Figure 4 is of poor quality, at least in the document at my disposal.

RESPONSE: The reference Martande et al is corrected in Table 2 and 3. Fonseca et al is corrected. Figures 3-7 are new.

Oum Keltoum Ennibi (Reviewer 3): Comments:

- To synthesize evidence regarding clinical effectiveness of systemic azithromycin (AZI) as adjunct to scaling-root planing (S/RSD) as compared to S/RSD alone in chronic periodontitis, and analyse potential moderators impacting heterogeneity in outcomes. This is the aim of the study and not a background

- references:
* in ref 2, 3 and 17 the journal is Periodontology 2000, so add 2000 in the references
* for ref 24, 26, 27, and 43, limit the number of author to 6 et al.
- figure 2b: please correct: detection

RESPONSE: The references are corrected in accordance with revisions

Best Regards

G Pelekos