Reviewer’s report

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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Reviewer: Peter Bottenberg

Reviewer's report:

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 for what should be done in clinical studies to improve reporting. Discuss the relevance for patients and public health of antibiotic adjuvants.

Further details: Martande 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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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No

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