Reviewer’s report

Title: Successful MDR-TB treatment regimens including Amikacin are associated with high rates of hearing loss

Version: 3 Date: 2 April 2014

Reviewer: Doosoo Jeon

Reviewer’s report:

WHO recently recommended extending the duration of injectable drug use from 6 to 8 months, as longer use of injectables has been found to be associated with more successful treatment outcomes. However, optimal duration of injectables, in terms of balancing the efficacy and adverse effects, is an important but controversial issue in MDR-TB treatment. In general, given the importance of the subject matter and the large number of patients included in the study, the manuscript makes a contribution to the field.

My specific comments are as below.

1. What is the valid denominator in the assessment of treatment outcomes (good vs poor)? Out of 437 MDR-TB patients 28% (n=124) were still on treatment. They were excluded in the primary and secondary analysis. However, according to the revised definition by WHO, majority of cases on treatment will be assigned outcome. In addition, the end of enrollment and observation is just same (June 30, 2012) in the manuscript (p7 line 28). I wonder whether majority of patients on treatment had the sufficient follow-up time for outcome analysis. I am not sure it would proper study design to include the patients still on treatment. Hopefully the authors can provide some explanation.

2. Did the authors assess the previous use of AG as a risk factor for hearing loss? Previous use of aminoglycoside is a known risk factor for ototoxicity. A total of 268 (61%) patient had treated with aminoglycosides prior to enrollment in this study. As shown in table 1, none of the patients with no documented hearing loss were previously treated with MDR-TB regimen, probably including aminoglycoside. Please clarify this issue and add some comments in the discussion section if necessary.

3. The authors should provide their policy and procedures for hearing test in detail in the method section. For example, how hearing was tested (facilities, testing equipment, methodology), how frequently it was performed, and, more importantly, what was the management strategies when hearing loss was found (stop the drug, reduce the dose, increase the dose interval, or retain current therapy while increasing the frequency of monitoring)?

Abstract

The numbers of patients who completed their treatment and had a good outcome
were inconsistent with those in table 1.

Methods

Study population

What does mean "censoring"? (p4 line 7, p7 line 27, and table 2)

Setting and procedure

1) add the method of drug susceptibility testing
2) add the reference to the WHO recommendation for amikacin dosage.
3) add the policy and procedures for hearing test as mentioned above.

Results

Cohort and study analysis

1) I hope the authors could provide clinical data briefly.
- drug resistance rate in the cohort, especially for AGs and FQs
- number of XDR-TB patients among the cohort

2) Clarify the denominator in the analysis of treatment outcomes and proportion of good and poor outcome in total cohort, as described in the abstract.

p8. line 11 "Those with no documented hearing loss, treatment success was 60 (60%) whilst 29(29%) were deceased." Why did the authors mention this sentence without mention of treatment outcome among patients with hearing loss? The authors wanted to show the poorer outcome for patients witout hearing loss compared to those with hearing loss? However, it was not comparable because 40% of patients without hearing loss were still on treatment.

Factors associated with amikacin-related hearing loss

- How many patients are tested with audiogram at baseline or during treatment?

Table 1.

1) provide each data in 'lost to follow up' and 'failure' group.
2) All abbreviations should be explained in a clear legend below the table.

Table 2.

1) This table is simple comparison between the groups rather than multivariate analysis. I think ' AOR(95% CI)' is typo.
2) Are there any significant difference between patients with and those without hearing loss? It would be better to add p-value in the table.
3) What does mean "censoring"?

4) I think 'average' is an ambiguous term. Does it mean 'median' or 'mean'?

Table 3

1) 'duration of amikacin treatment', 'average dose of amikacin',
What is the referent? The referent groups must be made clear for the odds ratios
presented. Without referent groups the odds ratios are not interpretable. I think it would be core data in the manuscript.

2) What does mean "predicts outcome perfectly"

Discussion

1. p10 line 2 "these recommended dosages may not apply to our population"
   It is hard for me to agree this sentence. Many factors including such as careful monitoring could be involved in ototoxicity.

2. The authors need to expand the discussion on why the incidence of ototoxicity is much higher in their cohort and how to minimize it.

Level of interest: An article of importance in its field

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

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.