Author's response to reviews

Title: Treatment of isoniazid-resistant pulmonary tuberculosis

Authors:

Yee Hyung Kim (yeehyung.kim@samsung.com)
Gee Young Suh (gysuh@smc.samsung.co.kr)
Man Pyo Chung (mpchung@smc.samsung.co.kr)
Hojoong Kim (hikim@smc.samsung.co.kr)
O Jung Kwon (ojkwon@smc.samsung.co.kr)
Song Yong Lim (symd21.lim@samsung.com)
Si Young Lim (siyoung.lim@samsung.com)
Won-Jung Koh (wjkoh@smc.samsung.co.kr)

Version: 3  Date: 22 July 2007

Author's response to reviews:

TO THE COMMENTS OF THE REVIEWER #1:

[filled right triangle] 1. In this retrospective study a 6-month regimen that consists of 2 months of therapy with INH, RIF, EMB, and PZA, followed by 4 months of therapy with INH, RIF, and EMB administered as daily therapy (2HREZ/4HRE) as a part of National tuberculosis program. The INH resistance was detected after 2 months in 64% patients just INH was withdrawn or PZA added in place of INH. So author should mention 2HREZ (actually administered) in place of 2REZ.

The correction was made as was recommended.

[filled right triangle] 2. When the subjects are sputum positive pulmonary TB with drug resistance, treatment completion rate should not be should not be the criteria of success. Definition of cure (conversion of sputum positive to negative at least at the end of the study) should be considered. Patient can remain sputum negative during the treatment period and can be sputum positive during end of the short course treatment. This is known as ‘fall and rise’ phenomenon, very common in drug resistant patients. Author should not consider ‘treatment completed’ patients from success rate.

Laserson et al. recently proposed standard definitions for treatment outcomes of MDR-TB. (Laserson et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005 Jun;9(6):640-5.) The definitions included "treatment completion". An MDR-TB patient who has completed treatment according to country protocol but does not meet the definitions for cure or treatment failure due to lack of bacteriologic results (i.e., fewer than five cultures were performed in the final 12 months of therapy) could be classified as "treatment completion".

In our study, the only one patient was classified as "treatment completion". The
patient was diagnosed as having culture-positive pulmonary TB by bronchoscopic examination. This patient could not expectorate sputum after the initiation of treatment. The radiographic abnormality in this patient disappeared completely after the treatment. The patient was not cured by definition because of lack of bacteriologic results. However, it was not practical to perform bronchoscopy in the end of treatment in this patient for the confirmation of bacteriologic conversion. Therefore, this patient was classified as a treatment success as was described in the Results section and Table 2 in our manuscript. The remaining 35 patients converted from culture-positive to culture-negative status after starting of treatment and remained culture-negative status. We clarified this information in the Results section.

[filled right triangle] 3. Two similar regimen (2REZ/7RE) and (2REZ/10RE). The intensive phase remained same in both the regimens only continuation phase were 7 months and 10 months respectively. The longer duration treatment has inferior result (71% vs. 100%). This result is surprising. This may be clarified.

We really apologize for our big mistakes. The value of 71%, 77%, and 100% meant the conversion rates after one month of treatment. The overall success rates were described in the revised version. However, the efficacies of various treatment regimens cannot be determined from our study, because the numbers of the patients who received the various regimens were insufficient for comparing the efficacy of the regimens and the assignment of the treatment regimens was not random. We added this information in the Discussion section.


We absolutely agree with your suggestions and the information was included in the Discussion section in the previously submitted manuscript. During the study period, however, the fluoroquinolones were not used in the treatment of INH-resistant pulmonary TB in our institutions. We added this information in the revised manuscript.

[filled right triangle] 5. Inclusion criteria (new case/ previously treated/default/relapse etc) should be clearly defined. Treatment history is very important for treatment drug resistant tuberculosis and should be mentioned broadly. Authors have mentioned same only 3 treatment failure cases. The information was added in the Results section and Table 1 as was recommended.

[filled right triangle] 6. Authors may mention the incidence and/or prevalence of
drug resistance (particularly to INH) in that geographical area.

We added the information in the Discussion section.

[filled right triangle] 7. The terms like 'cavitary consolidation' is inappropriate, may be changed

We used the term of "cavitary lesion' instead of "cavitary consolidation".

TO THE COMMENTS OF THE REVIEWER #2:

[filled right triangle] Major Comments: 1. This report suffers from two major problems: 1) it is retrospective and 2) it involves only 39 patients. However, treatment of INH resistant TB is still controversial as there have been relatively few randomized trials so additional information is potentially helpful.

We absolutely agree with your comments. This study has many important limitations. We really appreciate your many helpful suggestions.

[filled right triangle] 2. They define INH resistance as organisms resistant at 0.2 mcg/ml but a more conventional definition, or at least the definition felt to be clinically important, is resistance at INH concentrations of 1.0 mcg/ml. Could they add this information to Table 1 (See below for further suggestion for table 1).

The recently published review article discussed a problem associated with the antituberculosis drug susceptibility testing. (Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. Eur Respir J. 2005 Mar;25(3):564-9.) The author state that the difference in cumulative susceptible percentages between "probable susceptible" and "probable resistant" clinical isolates (at various concentrations) was greater at 0.2 mcg/mL with INH. In Korea, INH resistance was defined as organism resistant at 0.2 mcg/mL. We referenced this article in the Methods section.

[filled right triangle] 3. Two patients developed moderate hepato-toxicity - was this while they were on INH or on PZA, or did this develop while patients were taking only rifampin and ethambutol? This would be of interest because the hepato-toxicity of rifampin alone appears to be much lower than that due to the other TB drugs.

Two patients developed moderate hepatotoxicity during the initial phase of standard four-drug regimens (HREZ). We added this information in the Results section.

[filled right triangle] 4. The detailed case reports of three individuals with acquired drug resistance are not needed. This could be dropped in an effort to shorten the paper substantially.

We deleted the detailed case reports of three treatment failure cases as was recommended.
5. Compliance was defined as taking more than two-thirds of drugs each month. This is a rather lax definition of compliance and I wonder if they could provide more information on this point, particularly comparing the percentage of pills taken either each month or overall in the three who failed compared to the other smear positive patients who did not fail.

Our institutions did not perform directly observed therapy (DOT) like other institutions including health centers in Korea; rather, trained nurses checked the adherence of patients and called patients who did not show up for their monthly appointment. As you mentioned, compliance was defined as taking more than two-thirds of drugs each month in the submitted manuscript. That meant no patients broke their appointment schedule more than 10 days in every month. Actually, at least more than 90% of pills were taken overall in the three patients with treatment failure, although the exact percentage of pills taken could not be compared according the treatment outcomes.

6. The discussion is far too long. This entire paper should be shortened substantially and presented as a brief report, in light of the fact that it is retrospective and only 39 patients.

We deleted the abundant contents in the Discussion section as was recommended.

7. I suggest that Table 1 be modified and expanded slightly-please show two columns - the three who failed, compared to the 36 who did not. Please include details on the compliance as mentioned above and the INH resistance at 0.2 and at 1.0 if available in this Table.

We modified the Table 1 as was recommended. As mentioned in the above answers, the exact percentage of pills taken could not be compared according the treatment outcomes in this retrospective study. The INH resistance rate at 1.0 mcg/mL was not available in Korea.

8. Table 2 - please add information regarding those who are smear positive and smear negative, for each of the three treatment groups i.e. convert three treatment groups into six subgroups. Table 3 could be dropped.

Table 2 was modified as was recommended. In addition, Table 3 was deleted.

9. I note that almost all patients converted their sputum by two months and very few converted later. Even some of those who failed, converted their sputum to culture negative by the end of two months. Thus it is surprising to see three failures and this suggests to me that the problem was one of compliance rather than the drug regimens. Again, this can be examined more carefully by the authors, more information presented, and then this possibility should be discussed. This is particularly important in Korea where DOT is usually not practiced. In this series most patients, it appears were on self-administered
We did not consider the possibility of non-compliance as the reason of treatment failure in the three patients, although our institutions did not perform DOT. We did confirm the good compliance by repeated interview with the patients and the family members. However, we discussed the chance of non-compliance in the Discussion section.