Author's response to reviews

Title: Treatment of isoniazid-resistant pulmonary tuberculosis

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Author's response to reviews:

October 27, 2007

Dear Editor:

First of all, we appreciated all helpful comments of the reviewers regarding our manuscript entitled "Treatment of isoniazid-resistant pulmonary tuberculosis (Manuscript ID 1969953558126524)." We agreed to the points that the reviewers indicated and we revised the manuscript according to the points.

We hope that our reply and all changes we have made meet with your approval and look forward to your response.

Sincerely,

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TO THE COMMENTS OF THE REVIEWER #2:

- Major compulsory revisions
  1. Shortening: Previously I suggested a brief report, and I still recommend the same. Since the authors have not shortened this version of the paper, I suggest that they reduce it to 1500 words total. The major areas for shortening would be
the introduction, the results can be much briefer since all key results are in the tables. The discussion could be very substantially shortened.

We shortened this revised manuscript which contains 1,468 words excluding title, abstract, references and tables, as was recommended.

¿ 2. I had asked previously for information on the degree of INH resistance since they defined INH resistance as resistance at 0.2 microgram per ml whereas a more conventional definition is resistance at 1.0 microgram per ml. Please provide this information or an explanation why it is not available.

The reviewer insisted that a more conventional definition of INH resistance is resistance at 1.0 microgram per ml rather than 0.2 microgram per ml. However, we consider that a more conventional definition of INH resistance is resistance at 0.2 microgram per ml.

In 1994, the Global Tuberculosis Program of the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) initiated the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Since then, a global network of supranational reference laboratories (SRLs) was established to evaluate drug susceptibility test (DST) proficiency in countries implementing drug resistance surveillance. Procedures for DST conformed to one of several published methods: the absolute-concentration method, the resistance-ratio method, or the proportion method with solid medium or radiometric Bactec 460. In laboratories using the proportion method with solid medium, resistance was defined as at least 1 percent colony growth at critical concentrations of the drugs (i.e., 0.2 mg of isoniazid per liter, 2 mg of ethambutol per liter, 4 mg of dihydrostreptomycin sulfate per liter, and 40 mg of rifampin per liter). (Pablos-Mendez A, et al. Global surveillance for antituberculosis-drug resistance, 1994-1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med. 1998 Jun 4;338(23):1641-9.)

DST of the M. tuberculosis isolates in our study was determined by the absolute concentration method, using Löwenstein-Jensen medium, at the Korean Institute of Tuberculosis, which is the the WHO-designated SRL. The Department of Microbiology at the Korean Institute of Tuberculosis had conducted nine rounds of proficiency evaluation of DST between 1995 and 2003 for 16 national or regional laboratories in the Western Pacific Region of WHO. The drug concentration used to determine INH resistance in most of the laboratories is 0.2 microgram per ml rather than 1.0 microgram per ml. (Bai GH, et al. Proficiency Analysis of Drug Susceptibility Testing by the National-Level TB Laboratories from 1995 to 2003. J Clin Microbiol. 2007 Sep 12; [Epub ahead of print])

In addition, the recently published review article discussed a problem associated with the antituberculosis DST. (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 microgram per mL with INH. This was stated
in the previous response to Reviewers¿ Comments.

¿ Minor essential revisions:
I would like more information on the compliance of patients, particularly the three who failed.

As described in the Discussion section, both private hospitals including our institutions and public health centers in Korea did not perform directly observed therapy (DOT). Then, the possibility of poor compliance of treatment regimen could not be completely excluded in our patients. However, I am certain that the cause of treatment failure in three patients is not due to poor compliance. The three patients who failed are all my patients. I am confident of good compliance of these patients. This was confirmed by repeated interview with the patients and the family members. The three patients were also very compliant to the subsequent treatment regimens including second-line drugs.