Author’s response to reviews

Title: Serial Interferon-gamma Release Assays during Treatment of Active Tuberculosis in Young Adults

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Version: 2 Date: 29 July 2010

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Manuscript number: 1366527632399731

Dear Editor,

Thank you very much for giving us a chance to improve our manuscript. We revised our manuscript in accordance with the reviewers’ suggestions. We have underlined the revised or added texts. Our responses to the comments follow.

Reviewer 1

1. In the abstract – and throughout the MS – participants are described as having no-underlying disease. What is really meant is no underlying nontuberculous disease, and this is clarified at one point. However the initial impression given is that the participants were healthy (ie: without symptoms) which given that many of them had symptomatic TB, is confusing. This should be clarified.

► According to the suggestion, we clarified it in the section of ‘Demographic and clinical characteristics of the participants’ of Results. (Page 7)

“Every participant was negative for human immunodeficiency virus (HIV) and had no other underlying disease (e.g. uncontrolled asthma, diabetes mellitus, and chronic renal failure).”

2. On Page 6, the criteria for a positive result are given. While I would not change the manuscript, since this guideline was current at the time the study was done, I would note that this guideline is no longer current. See the most recent CDC release for the new guidelines, which have been developed in collaboration with Cellestis, who produce the QUANTiferon
We appreciate the reviewer’s kind information. As the reviewer suggested, we did not change the definition of positive QFT-GIT.

Reviewer 2

1. This is an interesting group of patients, as they were young, previously healthy and not immunocompromised military personnel. However in addition to those with pulmonary disease, there were eleven TB patients with pleuritis, one with lymphadenitis and one with TB abscess. It would be interesting to know how the QFT values changed in the patients with pulmonary disease, compared to those with pleuritis.

   In accordance with the reviewer’s suggestion, we compared the change of QFT values between patients with or without pleural effusion (figure 3). In addition, we discussed about the observed difference between them. (Page 10)

2. Multiple comparisons were corrected for using the Bonferroni correction – but in essence there are only single tubes that provide real data for the QFT result, as the PHA tube just provides a positive control, it is not clear if this is appropriate?

   We admit that the description of statistics was not perfect. We deleted unnecessary description (Page 6).

3. The median age was 21 years, but the range went up to 48 years. Might the younger subjects be expected to be experiencing a primary infection, whereas the older subjects might have been exposed to infection in the past and to be reactivating their disease? Can having an age of 48 years be described as “all young” (Page 10, third paragraph).

   As your suggestion, we mentioned “mostly young” instead of “all young”. (page 10)

4. The term negative reversion (Page 8, last two lines) is not ideal – patients must either show reversion or a lack of reversion. It could be replaced here and elsewhere by “reversion to
negativity” or “conversion to negativity” to make the meaning clearer.

► As the reviewer suggested, we replaced ‘reversion’ with ‘reversion to negativity’.

5. The term “sphericity” in the section on statistical analysis on page 6 should be explained.

► For repeated measures analysis of variance, the equal variance of the differences between levels of the repeated measures factor should be assumed, so called sphericity. We confirmed this by Mauchly’s test of sphericity. We explained it (page 6). In addition, because the sphericity was assumed and Wilks’ lambda was not applied in this study, we omitted unnecessary description (page 6, statistical analysis).

Additional Comment

Because the QFT-GIT ELISA cannot measure IFN-$\gamma$ values $> 10$ IU/ml accurately, we modified all IFN-$\gamma$ values $> 10$ IU/ml as 10 IU/ml in revised manuscript. We also describe this in methods section (page 6).

Thank you very much for insightful and thorough advice.

Yours sincerely,

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