Author’s response to reviewers

Title: In vivo expression of innate immunity markers in patients with mycobacterium tuberculosis infection

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Author’s response to reviewers:

Dear Professor

thank you for reviewing our manuscript. We highly appreciated your helpful comments. Appropriate modifications have been made to the manuscript according to the reviewers’ suggestions.

For further details please refer to the point to point argumentation below.

Reviewer: Gerhard Walzl

1. We totally agree with the reviewer, that these markers cannot replace the TST or the IGRAs. Our data support the hypothesis that Coronin-1, Sp110 and at least, Toll-like receptor-2, are involved in the infectious process of tuberculosis. However, their significance as markers of infection and their precise mechanism in human tuberculous infection deserve further investigation. According to reviewers’ suggestion, we removed the final sentence of the discussion, which is rather confounding.

2. In this study, patients with active tuberculosis in the lungs were documented by positive AFB staining of sputum smears in microscopy, and positive culture of sputum or BAL fluid. Patients with lymphadenitis were documented by positive AFB staining of the lymphnode aspirates. There was one pleural effusion which was diagnosed to be of TB origin by the ADA levels in the fluid and the compatible history of close contact to a case index, after having excluded all the other possible causes of pleurisy. There was one TB pericarditis which was documented by the history and the fluid characteristics. A sentence that clarifies this information has been added in the “MATERIALS AND METHODS” section,
in order this information to be clear in the text.

3. It might be possible that coronin-1 expression by peripheral blood mononuclear cells may indicate that these cells are carrying MTB, and/or that this expression is induced by the presence of pro-inflammatory host proteins. In this study this is a speculation that the design of the study does not permit to prove. However, Kreider et al (1) showed that haematogenous spread of tubercle bacilli during MTB infection occurs via blood vessels and lymphatics. Furthermore, Dannenberg et al. (40) showed that this spread occurs via a continuous turnover of macrophages between tuberculous lesions and the blood, a process that peaks during the phase of active infection.

4. The exposure time for close contacts identification, i.e the average daily exposure in hours multiplied by the days of exposure, during the last trimester preceding the tuberculosis diagnosis was also estimated according these CDC guidelines. This measure of exposure has also been validated in studies correlating the time exposure to an index case with the performance of the interferon gamma releasing assays (IGRAS) test. Airborne transmission of M tuberculosis is promoted by close and prolonged contact with an infectious person, and a key factor is the amount of time a contact spends sharing room air with an infectious individual. One set of criteria for estimating risk after exposure to a person with pulmonary TB without lung cavities includes a cut-off of 120 hours of exposure per month. Lalvani et al. assigned contacts to one of four predefined exposure categories; Category A: contacts (close and prolonged exposure) had lived in the same household or shared their workplace office with their index case. Category B: contacts (regular intermittent exposure) had been in the same room as their index case at least once per week for an estimated mean time of longer than 1 h (total) per week, for at least 4 weeks. Category C: contacts (casual intermittent exposure) had been in the same room as their index case for an estimated mean time of less than 1 h (total) per week. Category D: contacts had worked or studied in the same institution as an infectious person but had had no known contact with the index case or other tuberculosis patient.

1. Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis Recommendations from the National Tuberculosis Controllers Association and CDC MMWR. December 16, 2005/Vol. 54 /No. RR-15.


5. There are no studies in the Greek population estimating the QFT positivity rate. The QFT results are shown by Group in Table 1.

6. The time interval between diagnosis of TB and examination of household contacts was 1.5 month. Close contacts were assessed by TST and QFT at the time of TB diagnosis of the index case, and in those with negative results, the testing was repeated after 6 weeks. This clarification has also been added in the
7. A paragraph is added in the introduction section concerning the indication of QFT use in clinical practice.

8. Figures have been processed from the beginning.

9. The manuscript underwent grammatical and typographical editing.

Reviewer: Zahra Toossi

1. It might be possible that coronin-1 expression by peripheral blood mononuclear cells may indicate that these cells are carrying MTB, and/or that this expression is induced by the presence of pro-inflammatory host proteins. In this study this is a speculation that the design of the study does not permit to prove. However, Kreider et al (1) showed that haematogenous spread of tubercle bacilli during MTB infection occurs via blood vessels and lymphatics. Furthermore, Dannenberg et al. (40) showed that this spread occurs via a continuous turnover of macrophages between tuberculous lesions and the blood, a process that peaks during the phase of active infection.

2. Figures have been processed and redesigned from the beginning.

3. The manuscript underwent grammatical and typographical editing.

4. Editing of the sentences in pages 12 and 14 has been done, as proposed by the reviewer.