Author's response to reviews

Title: IP-10 response to RD1 antigens might be a useful biomarker for monitoring tuberculosis therapy

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Version: 3 Date: 6 April 2011

Author's response to reviews: see over
Dear Editor,

Please find enclosed the rebuttal letter for the manuscript “IP-10 response to RD1 antigens might be a useful biomarker for monitoring tuberculosis therapy” by Basirudeen Syed Ahamed Kabeer et al. to submit to BMC Infectious Diseases.

Please see below for the answers to the referees 2 and 3. We did not include the answers to referee 1 because he did not have further comments.

**Reviewer’s report-2**

**Title:** IP-10 response to RD1 antigens might be a useful biomarker for monitoring tuberculosis therapy

**Version:** 2  **Date:** 3 March 2011

**Reviewer:** Morten Ruhwald

**Reviewer’s report:**

The paper has been revised according to reviewer’s comments and has improved significantly. A minor revision of inconsistencies in terminology would improve readability.

**Discretionary comments:** Small letters after semicolons.

Abstract results. “unstimulated 1-day plasma” should read plasma of unstimulated 1-day whole blood culture or similar. Minor inconsistencies in terminology makes the paper unnecessarily difficult to access. Consistent wording would improve the readability.

**ANSWER:** we modified accordingly

p5l5 and p5l10 and elsewhere. “NIL”, “Nil” and “unstimulated “are used interchangeably.

**ANSWER:** we modified accordingly

p5l11 “QFT-IT antigens” defines the term but p7l4 used RD1 antigen-specific and p11l3 “QFT-IT” see also figure 2 “Blood” and “whole blood”

**ANSWER:** we modified accordingly

p11l16 “median” is missing

**ANSWER:** we modified accordingly

p12l14 the non-parametric test does not compare medians, suggest to delete.

**ANSWER:** we modified accordingly

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I am registered as inventor on patents disclosing IP-10 as a biomarker for TB infection.
Reviewer 3
Reviewer’s report
Title: IP-10 response to RD1 antigens might be a useful biomarker for monitoring tuberculosis therapy
Version: 2 Date: 27 February 2011
Reviewer: Payam Nahid
Reviewer’s report:
The authors have addressed my concerns from the first review. Even with a smaller, more refined set of 17 patients (16 of whom are culture confirmed), the changes in RD1-selected peptide stimulated IP10 and IFNg are significant. Interestingly, despite all patients being treated successfully at 6 months, some still have stimulated IP10/IFNg levels go up or stay unchanged, tempering any conclusions that one might wish to draw. As an exploratory study, these findings are interesting, but should be viewed as hypothesis generating and in need of a larger, better characterized cohort for confirmation. In light of these issues, I’d suggest that the authors further temper their conclusions (particularly in the abstract) by reiterating that these findings are hypothesis generating and need to be confirmed in a larger, well-characterized cohort of treated TB patients (much as they have stated at the end of the discussion). I highlight a few minor residual issues in the revision:

1) Methods, page 6 - middle of page: My read is that cases were defined microbiologically, either with sputum smears or culture, however, later on in the manuscript, the authors state that one case was a clinical diagnosis. Please clarify how a case was defined in the methods. Either include clinical diagnosis (without bacteriologic confirmation), or exclude the patient that was not culture or smear positive from analyses.
   ANSWER: we modified accordingly

2) Methods, page 6 - bottom of page: Please check spelling of rifampicin and pyrazinamide.
   ANSWER: we modified accordingly

3) Methods, page 7: In the response to reviewers, the authors state that IP10 was measured using a R&D kit, however, the methods continue to say a BD sciences kit was used. Please clarify.
   ANSWER: we modified accordingly

4) Results, page 10 - top of page: It would be more accurate to state that of 41 HIV-uninfected individuals previously described, 17 subjects met eligibility criteria for the study, and to state more clearly what the eligibility criteria were in the methods.
   ANSWER: we modified accordingly

5) Results, page 10 - top of page: Please provide the mean duration and range for treatment to be completed in the 17 patients. I understand that each patient
was initiated on a standard short course regimen, but how long did it take to complete?

**ANSWER:** we modified accordingly

6) Results, page 12- top of page: "When considering the highest IP-10 response to either ESAT-6 or CFP-10 selected peptides per single patient, the median IP-10 secretion was significantly higher at the time of diagnosis (median: 5116 pg/ml; IQR: 2207-7063) than at the end of treatment (T6) (median: 73 pg/ml; IQR: 0-5222) (p=0.0060)". Does this mean you compared highest IP10 response to either ESAT6 or CFP10 to the same antigen at T6, or did you compare the highest IP10 response to either ESAT6 or CFP10 at T0 to the lowest IP10 response to either ESAT6 or CFP10 at T6? Please clarify.

**ANSWER:** we always considered the highest IP-10 or IFN-γ response to either ESAT-6 or CFP-10 at T0 and T6 as well. We also added a paragraph in the MATERIALS AND METHODS section to clarify it.

I hope to have answered your questions and concerns.

I thank you for the valuable time you devoted to this manuscript and for the accurate comments that improved the quality of the text. I hope that the revised manuscript is now suitable for publication in the BMC Infectious Diseases Journal.

On behalf of all co-authors

Best regards,

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