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Modulation of IFN-gamma response to QuantiFERON TB-Plus detected by enzyme-linked immunosorbent assay in patients with active tuberculosis (TB), cured TB and latent TB infection

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Background: Interferon (IFN)-γ-release assays (IGRAs) are designed for the diagnosis of tuberculosis (TB) infection. The new IGRA called QuantiFERON®-TB Plus (QFT®-Plus) is based on enzyme-linked immunosorbent assay (ELISA) detection of IFN-γ following Myobacterium tuberculosis-antigen stimulation with TB1 and TB2 antigens. TB1 elicits a cell-mediated immune response by CD4 T-cells and TB2 elicits a response from both CD4 and CD8 T-cells (Petruccioli, J Infection 2016). Here, we characterize the variations of the values of the IFN-γ release detected by ELISA to the QFT®-Plus and the QuantiFERON®-TB Gold (QFT®) in patients with active TB, latent TB infection (LTBI) and cured TB.

Material/methods: We enrolled 165 individuals: 66 patients with active TB (47 microbiologically confirmed and 19 clinical diagnosed), 52 subjects with LTBI based on the positivity to QFT®-IT, 28 cured TB patients after successful treatment for active TB disease and 19 healthy donors. IFN-γ release detected by ELISA was concomitantly evaluated with QFT®-IT and QFT®-Plus kits. Mann Whitney test and Chi square test were used to find significant associations.

Results: All participants responded to mitogen stimulation. Among the active TB patients, 89% were scored positive to QFT®-Plus and 89% to QFT®. Among the LTBI patients, 98% were scored positive to QFT®-Plus and 100% to QFT®. Among the cured TB patients 75% were positive to QFT-Plus and 64% to QFT®-IT. None of the healthy donors responded to QFT® and QFT®-Plus.

Regarding the selective responses to TB1 and TB2, among those with LTBI, 98% responded concomitantly to TB1 and TB2 whereas among those with active TB only 83% and among those with cured TB 75%. In those with active disease, 5 were scored positive only to TB2 stimulation, whereas no LTBI subjects displayed similar profile ($p=0.04$). Interestingly, no patients with clinical TB diagnosis were scored positive only to TB2 stimulation. Moreover analyzing the results in terms of IFN-γ production, we found higher level of IFN-γ in response to TB1 stimulation ($p=0.0003$) or to TB2 ($p=0.0008$) in LTBI subjects compared to active TB patients.

Conclusions: We characterized the IFN-γ responses to QFT®-Plus antigens in participants with active TB, LTBI and cured TB. Similar sensitivity and specificity of QFT® and QFT®-Plus was detected in the all groups evaluated. Interestingly, after the successful therapy the number of QFT®-Plus and QFT® responders decreases, suggesting that the mycobacterial load influences the immune response. Moreover, patients responding only to TB2 stimulation are those with a microbiologically confirmed TB, reflecting the association between the mycobaterial load and the ability to stimulate a CD8 T-cell response. Higher levels of IFN-γ were found in LTBI compared to active TB probably reflecting the conserved ability to contain *M. tuberculosis* infection. These results are useful to understand the characteristics of the new QFT®-Plus test.