Modulation of CD4 and CD8 response to QuantiFERON-TB Plus in patients with active tuberculosis and latent tuberculosis infection followed over time during treatment

Teresa Chiacchioa, Elisa Petrucciolia, Ilaria Pepponi a, Valentina Vaninia, Gina Gualanob, Daniela Cirilloc, Fabrizio Palmierib, Giuseppe Ippolitod, Delia Golettia

a Translational Research Unit, Department of Epidemiology and Preclinical Research, National Institute for Infectious Diseases (INMI) “L. Spallanzani”, Rome, Italy
b Department of Clinical and Clinical Research, National Institute for Infectious Diseases (INMI), Rome, Italy
c Emerging Bacterial Pathogens Unit, Division of Immunology and Infectious Diseases IRCCS, San Raffaele Scientific Institute, Milan, Italy
d Scientific Direction, National Institute for Infectious Diseases (INMI), Rome, Italy

ABSTRACT

Objective/Background: Interferon (IFN)-γ release assays (IGRA) are designed for diagnosing tuberculosis (TB) infection. The new IGRA, Quantiferon-TB Plus (QFT-Plus), is based on the enzyme-linked immunosorbent assay detection of IFN-γ after stimulation with Mycobacterium tuberculosis TB1 and TB2 antigens. TB1 elicits a cellular-mediated immune (CMI) response by CD4 T cells, and TB2 contains peptides recognized by both CD4 and CD8 T cells. The aim of the study is to characterize the CMI to QFT-Plus peptides in active TB and latent TB infection (LTBI) at baseline and during or after specific treatment (follow-up).

Methods: We enrolled 7 individuals with active TB and 11 individuals with LTBI at baseline and followed them during the treatment, either for active diseases or preventive therapy. Peripheral blood mononuclear cells were stimulated with QFT-Plus antigens (TB1, TB2, and mitogen). Cytokine profile (IFN-γ, tumor necrosis factor-α, interleukin-2) and phenotype (CD45RA, CD27) of CD4 and CD8 T cells were characterized by flow cytometry.

Results: All the individuals responded to mitogen. CD4 T-cell responses to TB1 and TB2 were similar in both individuals with active TB and those with LTBI evaluated over time. Differently, we found a higher number of TB2-associated CD8 T-cell responders in individuals with active TB than in those with LTBI. For individuals with active TB, there was no change in the specific response overtime. Differently, in individuals with LTBI, the number of CD8 responders to QFT-Plus antigens increased during preventive treatment (TB1 = 5/11 [45%], TB2 = 5/11 [45%]) compared with that at the time of enrolment (TB1 = 1/11 [9%], TB2 = 1/11 [9%]). Moreover, we analyzed the effector memory profile of T cells responding to QFT-Plus antigens. The largest component of antigen-specific CD4 T cells (65%) had a

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* Corresponding author at: Translational Research Unit, Istituto Nazionale per le Malattie Infettive “L. Spallanzani” Via Portuense 292, 00149, Rome Italy. Tel.: +39 06 55170 954.
E-mail address: teresa.chiacchio@inmi.it (T. Chiacchio).
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central memory (CD45RA<sup>-</sup>CD27+) phenotype at enrolment and during follow-up. In contrast, specific CD8 T cells, which were analyzed only at follow-up because they were almost absent at baseline, were characterized by a large component with naïve (CD45RA<sup>+</sup>CD27+) phenotype (40%) and a minor component with central memory (25%) features.

**Conclusion:** To our knowledge, this is the first report characterizing CD4 and CD8 T-cell responses of individuals with active TB and with LTBI, followed overtime, to QFT-Plus antigens by flow cytometry. The results, although preliminary, may help in identifying better tools for monitoring therapy, especially in those with LTBI undergoing preventive treatment.

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**Conflicts of interest**

The authors have no conflicts of interest to declare.