The IFN-Gamma Release Assay ELISpot does not discriminate latent from active tuberculosis

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INTRODUCTION AND PURPOSE

The use of IFN-gamma Release Assays to detect Mycobacterium tuberculosis infection has been essentially approved for the diagnosis of primary infection (e.g., after exposure to contagion) or the detection of latent tuberculosis (e.g., before an immunosuppressive therapy). French regulation authorities recommended in 2011 not to use such IFN-based tests to diagnose active tuberculosis; however, the performances of these tests to discriminate latent from active tuberculosis have been poorly assessed.

We aimed to determine if the intensity of cellular immune response, reflected by the quantitative ELISpot assay, could be used to discriminate active from latent infection.

METHODS

All patients from our institution with a positive ELISpot tuberculosis assay (T-SPOT.TB®, Oxford Immunotec, England) were retrospectively included between November 2006 and April 2009, excepted the patients which ELISpot assays was performed before biologics (e.g., TNF-α antagonists) to detect latent tuberculosis.
In included patients, ELISpot was mainly performed as a part of the diagnostic procedure of a fever of unknown origin, and in contacts of patients with active tuberculosis.

Patients were categorized in 2 groups :
- active tuberculosis according to bacterial culture, pathology or therapeutic test ;
- latent tuberculosis otherwise.

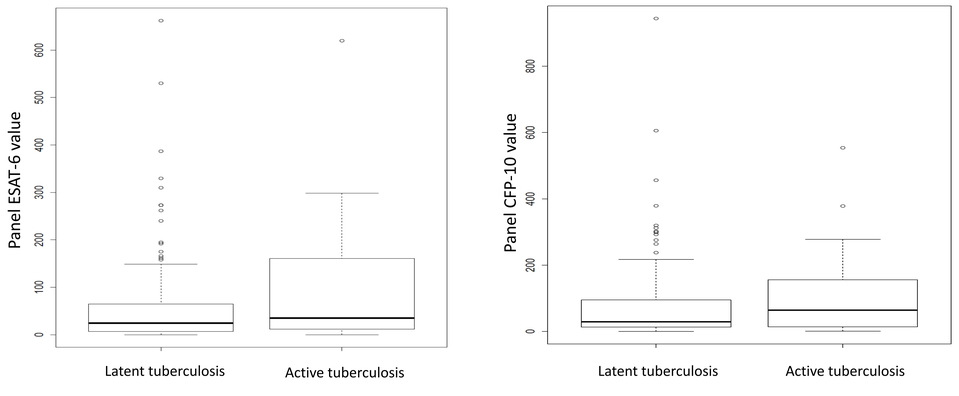
Mean number of spots with peptide panels ESAT-6 and CFP-10 were compared with Mann and Withney non-parametric test.
Receiver-operator characteristics (ROC) curves for peptide panels ESAT-6 and CFP-10 for the diagnosis of active *vs* latent tuberculosis were elaborated and the Area Under the Curve (AUC) calculated.

RESULTS (1)

Population
133 patients had a positive ELISpot assay (mean age 62 years).
99 patients (74,4%) were born in Europe. 24 patients (18%) were immunocompromised.
31 (23.3%) patients were diagnosed with active tuberculosis, among whom 13 had a positive bacterial culture. The other 102 patients were diagnosed with latent tuberculosis.

ELIspot performances
ELIspot values were not statistically different in patients with active or latent tuberculosis, either with peptide panel ESAT-6 (93.1 *vs* 67.5 spots, p=0.19) or peptide panel CFP-10 (111 *vs* 87.5, p=0.19) (figure 1).
The difference was still not significant when comparing only the culture-positive cases with latent tuberculosis cases (43.1 *vs* 67.5 spots [p=0.9] for panel ESAT-6 and 105.4 *vs* 87.5 [p=0.12] for panel CFP-10).

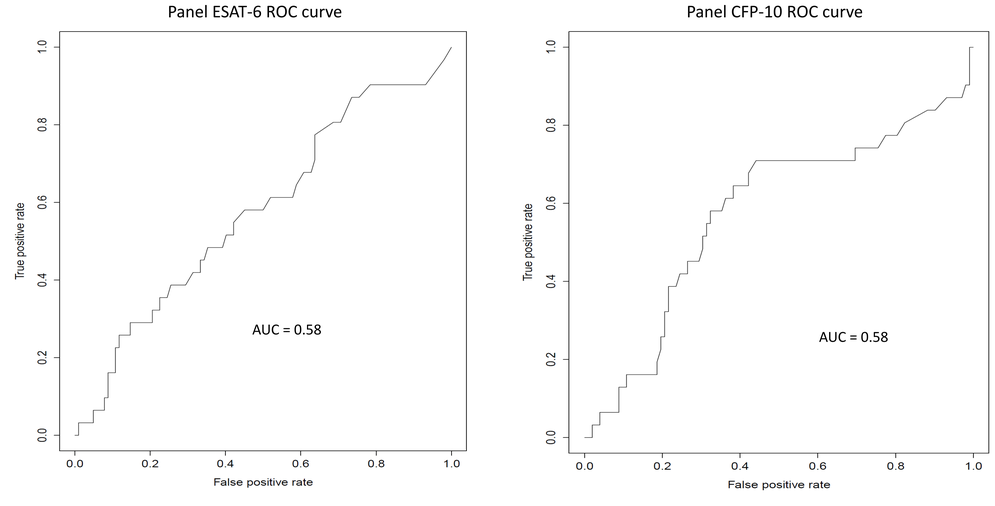
Figure 1 : ELIspot values of peptide panels ESAT-6 and CFP-10



RESULTS (2)

Area under curve of ROC curve was low (0.58) for both peptide panels (figure 2).

Figure 2 : ROC curves for peptide panels ESAT-6 and CFP-10



CONCLUSIONS

When an ELISpot assay is positive, the number of spots cannot be used to discriminate latent from active tuberculosis.
Consistently with previous works establishing that sensibility and specificity of IFN-gamma release assays are not high enough to recommend their use to diagnose active tuberculosis, our study confirms that they must not be used, even as a quantitative test, in this indication.

References
- *Tuberculose et tests de détection de l'interféron-γ, rapport du Haut Conseil de la Santé Publique*, July 2011, France
- National Institute for health and Care Excellence guideline 117: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control, March 2011, UK.