

Use of Gamma-interferon assays in low- and medium-prevalence countries in Europe – a consensus statement of a Wolfheze Workshop organized by KNCV Tuberculosis Foundation / EuroTB, Vilnius September 2006.

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Interferon gamma release assays (IGRA) offer an alternative to tuberculin skin testing (TST or Mantoux) for the diagnosis of tuberculosis (TB) latent infection (LTBI) or as an additional diagnostic method for active TB [1-3].

Two detailed guidelines, one from the Centers for Disease Control, USA (CDC) [4] and the other from the UK National Institute for Clinical Excellence, [5] have been produced on the appropriate use of novel gamma interferon assays (IGRA) for the diagnosis of TB infection (LTBI) and active TB. In considering these guidelines, two commercial systems the T Spot (Oxford Immunotec, UK) and Quantiferon Gold (Cellestis, Australia) were considered.

Public health specialists involved in TB control, mainly in low and intermediate TB incidence European countries met in Vilnius, Lithuania in September 2006, to consider the use of IGRA assays against the background of these two guidelines and increasing demands for the use of these assays. The group did not feel that it was necessary to write their own guidelines but rather to emphasise the main points of agreement with the published guidelines.

This statement represents a consensus of the group. As the field is rapidly evolving the group felt that this guidance should be kept under regular review as new data becomes available.

For the diagnosis of latent TB infection:

- There was consensus on the value of the use of these tests for the diagnosis of LTBI as described in the two guidelines [4,5] based on the following agreed points:
- Although there is no clear gold standard for LTBI, IGRA positivity in published contact tracing incidents reflect the degree of exposure to infectious cases more accurately than does TST. This suggests that IGRAs are more specific than TST. Discordant results between IGRAs and TST, however, cannot be completely explained by the notion that IGRAs are more specific with regard to cross-reaction with NTM infections or BCG.
- Both commercial systems probably perform as well as each other for LTBI detection in immunocompetent individuals.
- Studies of IGRA sensitivity suggest they are at least as sensitive as TST in TB patients but less sensitive than TST for detecting LTBI.
- Theoretically combining TST (with its high sensitivity) followed by IGRAs with their greatest specificity should be an optimal approach for contact tracing in incidents where there is a **known** index or source case. Clearly this advantage is negated where the patient does not return for reading of the TST and the single-visit IGRA would then be more advantageous.
- Although it is reasonable to assume that a positive IGRA is as predictive of later active TB as a positive TST, there is no evidence so far to suggest a higher or lower degree of predictability (see future work).

- IGRAs are of value for diagnosing/excluding LTBI in children or HIV positive (or other immunocompromised individuals), and those about to receive anti-Tumour Necrosis Factor or other immunomodulating therapy..
- IGRAs are of value in any situation requiring serial TST testing eg occupational health related screening/exposure (as there is no booster effect).

Future work: The group felt that further work was needed as follows:

- In low and intermediate incidence environments longitudinal studies are needed to establish the real probability of a positive IGRA leading to active TB. This is challenging but this should not delay the use of these tests in general.
- It is not clear that IGRAs and TST are measuring the same pool of immunological effector cells and further analysis of the underlying immunology is required.
- Test reproducibility should be addressed by studies of serial examinations of infected individuals. Apparent reversion of positive infection is known to occur in a small number of individuals but the meaning of this reversion is unclear.

Active TB:

- IGRAs are of value in diagnosing active TB (but should **NOT** replace appropriate microbiological and molecular investigation). IGRAs have **no** benefit in known pulmonary TB cases with bacteriological/molecular confirmation.
- Studies have shown variable but generally high sensitivity (75-97%). Sensitivity may be slightly reduced by active disease, as TST is reduced by anergy in severe disease.
- Specificity is very high (90-100%) (where there is no evidence of previous active TB). IGRAs do not cross react with BCG but cross-react with a small number of non-tuberculous mycobacteria.
- IGRAs would have the greatest *potential* benefit in the diagnosis of TB in difficult to diagnose cases such as those in children, those in the immunocompromised such as in HIV positive individuals and extra-pulmonary TB (especially TB meningitis).
- There is evidence for the use of IGRAs to diagnose active TB in children and in HIV positive individuals but little for extra-pulmonary TB at this time.
- Overall both tests perform similarly but the T spot may be more sensitive in HIV positive and severely immunocompromised individuals and has fewer indeterminate results but this may be due to the current cut-offs used for these tests (see future work). Conversely the Quantiferon assay is easier to perform and is less time-sensitive.

Future work: The group felt that further work was needed as follows:

- More carefully designed head to head studies are needed in general particularly for hard to diagnose groups (children, HIV positive and other immunocompromised individuals and in those with extra-pulmonary TB particularly TB meningitis).
- Analysis of cut-offs used in both assays and consideration of different cut-offs for different patient groups is needed.
- Test reproducibility should be addressed by series of repeated or sequential examinations of patients and exposed persons.

There is a place for IGRAs for both the diagnosis of latent infection and active TB; their use should be carefully considered in relation to the value likely to be brought to the individual and to the public good.

References

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