

Short reports

POSITION STATEMENT ON INTERFERON- γ RELEASE IMMUNOASSAYS IN THE DETECTION OF LATENT TUBERCULOSIS INFECTION, OCTOBER 2007

National Tuberculosis Advisory Committee

Detection and treatment of latent tuberculosis infection (LTBI) is considered to be an increasingly important element of tuberculosis (TB) control efforts in Australia and other low incidence countries. *In vitro* T-cell based interferon- γ release immunoassays (IGRAs) are marketed as a substitute for the tuberculin skin test (TST) for the detection of LTBI. The specificity of these immunoassays has been optimised by utilising pooled synthetic antigens, such as early secretory protein 6 [ESAT-6] and culture filtrate protein 10 [CFP-10], from the *Mycobacterium tuberculosis*-specific region of difference 1 (RD1) region and has been recently reviewed (Pai et al, 2004; Menzies et al, 2007).

Data suggest that IGRAs using these antigens are more specific than TST, having less cross-reactivity with previous Bacille Calmette-Guérin (BCG) immunisation or exposure to non-tuberculous mycobacteria, potentially offering distinct advantages for the detection of LTBI. However, the assessment of the sensitivity of IGRAs for diagnosing LTBI in differing environments and countries is complicated by the lack of a gold standard for diagnosing LTBI, the varied methodology across studies in the performance of TST and the interpretation of TST reactions, and the limited long-term follow-up of those subjects tested with IGRAs compared with the historical data available on those populations tested with TST. There is also limited data on the use of these immunoassays in certain sub-populations such as immunocompromised patients, children, and populations from TB-endemic countries, although such data on these populations are emerging for one or both of the two commercial IGRA *in vitro* tests currently available. Additionally, long-term follow-up studies are underway and will help clarify issues relating to the performance characteristics of IGRAs. As such information is carefully reviewed, the performance characteristics and clinical interpretation of these immunoassays will become better defined. Furthermore, the National Tuberculosis Advisory Committee (NTAC) feels that the performance, utility and cost effectiveness of IGRAs remain to be defined under Australasian TB program conditions. Finally, populations most

in need of access to accurate diagnosis and potential treatment of LTBI are often in remote and other community centres distant from laboratory services, or are the groups for which the IGRA tests are currently assessed to be least reliable, i.e. children and the immunosuppressed (although for the latter group, TST is also unreliable).

Both NTAC and state-based TB services encourage further clinical and economic evaluation of IGRAs. NTAC considers that the role of IGRAs in diagnosing LTBI will be better defined by:

- ongoing comparative studies of TST and interferon- γ assays undertaken by staff specially trained in the standardised application of the TST, where results can be compared as both continuous and dichotomous variables to assess suitable positive/negative cut-off scores, as well as to further investigate sensitivity, specificity and discordant results;
- sequential testing of IGRAs on various patient groups to characterise and quantify conversion and reversion reactions;
- further research on the use of IGRAs in children;
- independent cost-benefit analysis on the use of IGRAs using states' and territories' preferred protocols of investigating LTBI in Australia. Such analysis is needed to investigate the relative economic outcomes of changing from TST to immunoassays taking into account the structure of TB services and program delivery in Australia; and
- comparison of alternative IGRAs to determine differences between the assays.

NTAC suggests the research and rollout questions summarised in the December 2005 Morbidity and Mortality Weekly Report (Mazurek et al, 2005) paper from the United States Centers for Disease Control and Prevention and recent review article by Pai (Pai et al, 2007) could act as a basis for future investigations.

In summary, NTAC makes the following recommendations:

- currently TST remains the preferred method of screening for LTBI pending further evaluation of IGRAs;
- TST and IGRAs have almost no place in the diagnosis of active TB disease;
- state-based TB services should be encouraged to participate in the evaluation of the role of IGRAs for the investigation of LTBI; and
- IGRAs may be used as a supplementary test in individualised clinical assessment for LTBI where increased specificity is valuable in reducing the confounding effect from prior BCG vaccination or prior exposure to non-tuberculous mycobacteria.

In making these recommendations, NTAC recognises that IGRAs are a novel test for a disease with a delayed onset where the 'gold standard' comparator test (i.e. TST) is imperfect. The NTAC position statement and recommendations will be under ongoing review and will be revised as new peer-reviewed published data becomes available. NTAC is committed to ongoing monitoring of new diagnostic tests that may be of value in TB control.

References

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