Repeated tuberculin testing does not induce false positive ELISPOT results

The Enzyme Linked ImmunoSpot (ELISPOT) is a new rapid T cell based blood test (otherwise known as an interferon-γ assay) for the diagnosis of latent tuberculosis infection. 1 The commercially available form of the assay, T-SPOT® TB (Oxford Immunotec, Abingdon, UK) has European regulatory approval as an in vitro diagnostic test and is increasingly being used in clinical practice. The test is based on the enumeration of interferon-γ producing T cells which are specific for two highly antigenic proteins, early secretory antigenic target-6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These proteins are expressed by Mycobacterium tuberculosis but are absent from M bovis BCG vaccine. Hence, the test does not give false positive results in BCG vaccinated individuals.1,2,3

ESAT-6 and CFP-10 are, however, contained within tuberculin purified protein derivative (PPD). Since ELISPOT is a highly sensitive method for measuring even low numbers of antigen specific T cells,4 concerns have been raised as to whether repeated tuberculin skin tests might induce T cell responses to these specific antigens, resulting in false positive ELISPOT results.

As T-SPOT® TB enters clinical practice, it may initially be used by some people in conjunction with the tuberculin skin test. It is therefore important to know whether false positive ELISPOT results are induced by tuberculin testing. The following results strongly suggest that this is not the case. The results reported here are from a 2 year follow up of a group of people with potential point source exposure to multidrug resistant tuberculosis.8 Of the 2312 patients randomised to LABA (184 patients experienced one or more moderate or severe exacerbations), one less will experience an exacerbation. The corresponding number needed to treat (NNT), as was done for every 37 patients receiving LABA in the earlier study, 184 experienced one or more moderate or severe exacerbation was 1.35 times higher in those receiving a higher dose of ICS than in those treated with LABA. Unfortunately, it is difficult to draw any meaningful conclusion as to the clinical relevance of these findings or to compare at a glance the results with those of the previous MIAwMA study4 because of differences in the summary statistics presented. We believe that in order to understand the clinical context of these two studies, it is helpful to calculate the number needed to treat (NNT), as was done in the original MIAwMA study.

We read with interest the meta-analysis by Masoli et al5 which aimed to further guide clinicians in their choice between addition of long acting β2 agonists (LABA) or use of higher doses of inhaled corticosteroids (ICS) in patients with symptomatic asthma. The pooled odds of at least one moderate or severe exacerbation was 1.35 times higher in those receiving a higher dose of ICS than in those treated with LABA. The high sensitivity of the ELISPOT assay for detecting even low numbers of antigen specific T cells, the absence of a detectable response to ESAT-6 and CFP-10 suggests that T cells specific for these antigens were not induced by repeated inoculation of PPD. This is consistent with the observation that ESAT-6 has very poor immunogenicity when presented to the immune system during natural M tuberculosis infection; indeed, ESAT-6 is the strongest known target of T cell responses during tuberculosis infection.4

Further results also suggest that T-SPOT® TB could be especially useful in distinguishing true latent tuberculosis infection from false positive tuberculin skin test results that have arisen through “boosting”. Boosting occurs in people who undergo repeated tuberculin skin tests (such as healthcare workers) and causes false positive skin test results in uninfected people. This phenomenon is a major problem in tuberculosis screening programmes for healthcare workers, prison- ers, and other groups at persistent risk of tuberculosis exposure, and was almost certainly the reason why three individuals in our study developed positive skin test results after repeated testing. Our findings suggest that T-SPOT® TB will maintain its high specificity even in individuals with false positive skin test results due to boosting from repeated tuberculin testing. Thus, use of T-SPOT® TB could enhance our ability to screen for latent tuberculosis infection even in populations who have already been repeatedly screened by the skin test.

L Richeldi Respiratory Disease Clinic, University of Modena and Regina Emilia, and Azienda Ospedaliera Polyclinica di Modena, Modena, Italy

K Ewer Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

M Losi, P Roversi, L M Fabbri Respiratory Disease Clinic, University of Modena and Regina Emilia, and Azienda Ospedaliera Polyclinica di Modena, Modena, Italy

A Lalvani Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

Correspondence to: Dr A Lalvani, Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK; a.lalvani@nmd.ox.ac.uk

The study was approved by the Modena research ethics committee and each study participant provided written informed consent. doi: 10.1136/thx.2005.049759

This work was supported by the Wellcome Trust and Azienda Ospedaliera Polyclinica di Modena.

Competing interests: AL is a named inventor on patents relating to T cell based diagnosis filed by the University of Oxford. Regulatory approval and commercialisation of ELISPOT (T-SPOT TB) has been undertaken by a spin out company of the University of Oxford (Oxford Immunotec Ltd), in which AL has a share of equity and to which he acts as scientific advisor in an executive capacity. KE is a named inventor on a patent application relating to the application of ELISPOT filed by the University of Oxford. The University of Oxford has a share of equity in Oxford Immunotec Ltd.

Clinical importance of the Step 3 choice in asthma

We read with interest the meta-analysis by Masoli et al5 which aimed to further guide clinicians in their choice between addition of long acting β2 agonists (LABA) or use of higher doses of inhaled corticosteroids (ICS) in patients with symptomatic asthma. The pooled odds of at least one moderate or severe exacerbation was 1.35 times higher in those receiving a higher dose of ICS than in those treated with LABA.


Figure 1 Time course of development of positive Mantoux results in the three participants who became tuberculin skin test (TST) positive as a result of repeated skin testing.

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L Richeldi, K Ewer, M Losi, P Roversi, L M Fabbri and A Lalvani

Thorax 2006 61: 180
doi: 10.1136/thx.2005.049759

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