From latent to active TB: are IGRAs of any use?

Wei Shen Lim

In May 2014, the World Health Assembly approved the WHO End TB Strategy which set ambitious targets for the elimination of tuberculosis (TB), including a 95% reduction in TB deaths and a 90% reduction in TB incidence by 2035.[1] In December 2015, WHO Guidelines for low-TB-burden countries for the management of latent *Mycobacterium tuberculosis* (MTB) infection (LTBI) were published in support of the WHO End TB Strategy.[2] A major focus of these guidelines is the identification of people with LTBI and the provision of chemoprophylaxis to prevent the development of active TB in those infected.

Latent TB infection is defined as a state of persistent bacterial viability, immune control and no clinical evidence of active TB.[3 4] There is no direct test to diagnose LTBI. Instead, LTBI is recognised by the presence of measurable immune sensitisation to MTB as identified by a positive result to either tuberculin skin testing or an interferon-γ release assay (IGRA).[5] In many high-income and upper-middle-income countries with low TB incidence, IGRAs currently play an integral part in screening programmes for LTBI. A clear understanding of the predictive value of IGRAs for the development of active TB disease is therefore necessary.

In 2012, Rangaka *et al*[6] published a meta-analysis of longitudinal studies that assessed the positive and negative predictive values (PPVs and NPVs) of IGRAs for future active TB. Fifteen studies (6 from Europe) with a combined sample size of 26 680 participants were analysed; the largest study followed up 5676 individuals. Over a median follow-up period of 3 years, an incidence of active TB of 2 to 24 per 1000 person-years for IGRA-negative persons, compared with 4 to 48 per 1000 person-years for IGRA-positive persons was noted.

Hermansen *et al*[7] report results from a large 5-year nationwide retrospective registry study comprising 15 980 individuals with a minimum of 2 years follow-up. The study is remarkable for including almost all individuals in Denmark who had an IGRA test (QuantiFERON-TB Gold In-Tube test (QFT)) performed during the study period. Reasons for testing were not captured in the register and therefore, while it is expected that testing occurred in line with national recommendations, the proportions tested as part of (a) contact tracing, (b) screening before initiation of immunosuppressive treatment and (c) investigations to diagnose TB could not be reported. Precise data on chemoprophylaxis were also unavailable for the majority of individuals; the authors estimate isoniazid chemoprophylaxis coverage of approximately 35% in Denmark based on other available data sources. As regards outcome, the diagnosis of TB was based on positive microbiology (culture/PCR/microscopy) in 70%–75% of cases, or on clinical criteria alone. These study characteristics mean that results could not be reported according to risk groups nor chemoprophylaxis status, thus raising uncertainty around the reported PPV as an estimate of the true PPV for predicting active TB using the QFT assay. Incorporation bias (when the diagnostic test under consideration is used to determine the outcome) and partial verification bias (when individuals with positive tests are more likely to be subject to a 'gold standard' diagnostic) may also have influenced results.[8]

These limitations aside, the study by Hermansen *et al* provides valuable information on the test characteristics of the QFT assay as it is used operationally and complements results from two other large European studies that have been published recently; Zellweger *et al*[9] reported a prospective cohort study conducted by the TB Network European Trials Group involving 5020 contacts of TB index cases from 10 countries, while Sloot *et al*[10] from Amsterdam reported a 10-year retrospective cohort study of 9332 contacts of pulmonary TB (see table 1 for summary of results).

Taken together, these three studies affirm that in low-TB-incidence countries

A. the majority (>95%) of patients screened according to current national guideline recommendations do not go on to develop active TB regardless of chemoprophylaxis status;
B. a negative IGRA has a very high NPV for future active TB (>99.5%);
C. a positive IGRA has a low PPV for future active TB (<4%).

In the studies by Zellweger *et al*[9] and Sloot *et al*,[10] the provision of chemoprophylaxis for patients with a positive IGRA was associated with lower rates of incident TB. Zellweger *et al* estimated that the number needed to treat to prevent one case of incident TB among close contacts was 37 using the T-SPOT.TB test and 38 using QFT.

What then is the message for clinicians? The consistently high NPV with a negative IGRA is highly reassuring and strongly supports existing recommendations that chemoprophylaxis is not required for these individuals. On the other hand, the low PPV with a positive IGRA underlines the weakness of IGRA testing in isolation as an instrument for discriminating who will go on to develop active TB. An assessment of other factors (age, nature of exposure, immune status) aids refinement of the risk and indeed, such individualised decision making is carried out daily by front-line TB clinicians.

Possible reasons for the poor predictive value of IGRAs are helpfully summarised in a recent comprehensive review by Pai *et al*.[11] The generally low overall risk of progression from LTBI to active TB (outside certain high-risk groups) does

Table 1 Comparison of three recent European studies

Study authors	Zellweger *et al*[9]	Sloot *et al*[10]	Hermansen *et al*[7]
Population screened	Close contacts (n=5020)	Close contacts (n=4774)	Mixed, nationwide (n=15 980)
IGRA positive, n (%)	1367 (27)	739 (16)	1703 (10.7)
CP given in IGRA pos, n (%)	971 (58%)	309 (45%)	Not known
Incident TB			
IGRA pos, no CP (%)	3.5	2.7	–
IGRA pos, with CP (%)	0.4	1.2	–
IGRA pos (%)	–	–	1.3
IGRA neg (%)	0.15	0.09	0.14

CP, chemoprophylaxis; IGRA, interferon-γ release assay; neg, negative; pos, positive.

Correspondence to Dr Wei Shen Lim, Nottingham University Hospitals NHS Trust, City Hospital Campus, Nottingham NG5 1PB, UK; weishen.lim@nuh.nhs.uk

mean that even a perfect test for LTBI will have a low PPV. In addition, the immune response as measured by IGRAs is also the same response preventing progression to active TB. More specifically, current IGRAs are dependent on only a few antigens encoded by genes located within the region of difference 1 locus of the MTB genome—early secreted antigenic target 6 and culture filtrate protein 10. However, antigens expressed by MTB during latency versus replication may differ. An ongoing challenge for researchers is, therefore, the development of improved means for identifying individuals at risk of developing active TB and who would benefit from chemoprophylaxis; measuring the interferon-γ response alone may not be sufficient.

As testing for LTBI is coupled with the provision of chemoprophylaxis, the likelihood of non-adherence to and adverse effects from therapeutic agents are important further considerations at the clinical interface. Adverse event rates from current chemoprophylaxis regimens are in the region of 8%.[12] Although this is relatively low, most individuals with LTBI have no symptoms and even such low event rates may not be widely acceptable. Some evidence suggests that chemoprophylaxis completion rates are inversely associated with duration of therapy (6-month isoniazid vs 3-month or 4-month rifampicin containing regimens) and that non-adherence is associated with higher risks of developing active TB compared with individuals who complete treatment.[12 13] Improved diagnostics, better therapeutic agents with fewer adverse effects and shorter treatment regimens are all needed.

In the meantime, we should make the best use of available tools, imperfect though they may be. The wide variation in reported chemoprophylaxis rates for LTBI in different patient groups across countries with low TB incidence suggests that further improvements can be pursued.[14] In the UK, the updated National Institute for Health and Care Excellence (NICE) Tuberculosis Guideline (NG33) published in January 2016 should facilitate such improvements.[15]

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Lim WS. *Thorax* 2016;**71**:585–586.

▶ http://dx.doi.org/10.1136/thoraxjnl-2015-208228

Thorax 2016;**71**:585–586.
doi:10.1136/thoraxjnl-2016-208955

REFERENCES

1 Uplekar M, Weil D, Lonnroth K, *et al*. WHO's new end TB strategy. *Lancet* 2015;385:1799–801.
2 Getahun H, Matteelli A, Abubakar I, *et al*. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J* 2015;46:1563–76.
3 Getahun H, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis Infection. *N Engl J Med* 2015;373:1179–80.
4 Mack U, Migliori GB, Sester M, *et al*. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. *Eur Respir J* 2009;33:956–73.
5 Salgame P, Geadas C, Collins L, *et al*. Latent tuberculosis infection—revisiting and revising concepts. *Tuberculosis (Edinb)* 2015;95:373–84.
6 Rangaka MX, Wilkinson KA, Glynn JR, *et al*. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12:45–55.
7 Hermansen TS, Lillebaek T, Langholz Kristensen K, *et al*. Prognsotic value of interferon-gamma release assays, a population-based study from a TB low-incidence country. *Thorax* 2016;71:652–8.
8 Kohn MA, Carpenter CR, Newman TB. Understanding the direction of bias in studies of diagnostic test accuracy. *Acad Emerg Med* 2013;20:1194–206.
9 Zellweger JP, Sotgiu G, Block M, *et al*. Risk assessment of tuberculosis in contacts by IFN-gamma release assays. A Tuberculosis Network European Trials Group Study. *Am J Respir Crit Care Med* 2015;191:1176–84.
10 Sloot R, Schim van der Loeff MF, Kouw PM, *et al*. Risk of tuberculosis after recent exposure. A 10-year follow-up study of contacts in Amsterdam. *Am J Respir Crit Care Med* 2014;190:1044–52.
11 Pai M, Denkinger CM, Kik SV, *et al*. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. *Clin Microbiol Rev* 2014;27:3–20.
12 Erkens CG, Slump E, Verhagen M, *et al*. Monitoring latent tuberculosis infection diagnosis and management in the Netherlands. *Eur Respir J* 2016;47:1492–501.
13 Morán-Mendoza O, Marion SA, Elwood K, *et al*. Tuberculin skin test size and risk of tuberculosis development: a large population-based study in contacts. *Int J Tuberc Lung Dis* 2007;11:1014–20.
14 D'Ambrosio L, Dara M, Tadolini M, *et al*. Tuberculosis elimination: theory and practice in Europe. *Eur Respir J* 2014;43:1410–20.
15 National Institute for Health and Care Excellence. Tuberculosis: prevention, diagnosis, management and service organisation (NICE guideline 33). 2016. http://www.nice.org.uk/guidance/ng33