COMMENTARY

Screening Latent Tuberculous Infection To Treat: Not So Straightforward

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It is obvious that active tuberculosis (TB) disease must be fully treated with at least 6 months' of anti-TB medications. What is less clear and inconsistently practiced is the screening and treatment of latent TB infection (LTBI). Swarna Nantha, in a review article published in this issue of MJM,[1] appeals for targeted case screening of LTBI in certain high risk populations particularly our diabetic population that has a higher than average prevalence and trend compared to many countries[2]. Many of these patients have renal disease and are living longer, both of which compounds on the risks of LTBI progressing to active disease. The author also reviews the utility of Interferon-γ Release Assays (IGRAs) that has received much attention as a diagnostic tool for LTBI and has advantages over the tuberculin skin tests (TST) like Mantoux test.

It is true that a huge gap in global TB control today is the eradication of TB reservoir in human population. WHO estimated that one third of world's population is infected with mycobacterium tuberculosis[3]. However only 5-10% of infected individuals develop active disease over their lifetime. The rest remain healthy and are labeled as latently infected individuals. Factors influencing the clearance of pathogen and disease progression are not fully understood[4,5]. Recognized risk factors include HIV infection, immunosuppressive treatment like corticosteroids, anti-TNF therapy, anti-cancer treatment, malnutrition, malignancy, alcoholism, renal failure and insulin dependent diabetes,[6,7,8] Specific cause of reactivation in the majority of cases remains elusive[4]. From a clinical and public health perspective, screening and treatment of LTBI should target these at risk population since it makes no sense to treat everyone of LTBI. Swarna Nantha's call to screen diabetic population in Malaysia seems sensible in the wake of such high prevalence we have.

The challenge however lies in the lack of a gold standard to diagnose LTBI. TST and IGRAs are at best test of immune recall. They inform us that infection has occurred but not necessarily proved that it persists[9]. IGRAs is certainly superior to tuberculin skin tests as they are tests of IFN-γ response from T cells of sensitized individuals after stimulation commonly with ESAT-6 and CFP-10, two secretory proteins released by a key genomic loci of tubercle bacilli that enhance mycobacterial virulence[10]. This response is potent, specific and does not occur in BCG strains and most atypical mycobacteria[11]. They also have the advantage of being a single test with quantifiable measurements, unlike Mantoux test that requires two separate visits for interpretation and is subjected to observer bias. Currently in the market, there are QuantiFERON-TB Gold (QFT-G) and QuantiFERON-TB Gold In-Tube test (QFT-GIT) (Cellestis Ltd, Carnegie, Australia) and T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK).

Bearing in mind of this lack of gold standard, the pivotal question is how we can best utilize these tests of immune recall to conclude that one has LTBI and to treat accordingly. A meta-analysis of 38 studies showed the pooled sensitivity of 78% (95% CI, 73–82%) for QFT-G, 70% (CI, 63–78%) for QFT-GIT and 90% (CI, 86–93%) for T-SPOT.TB assay[12]. These tests may be reduced in HIV-infected individuals[13] but do not appear to be affected by immunosuppressive therapies in patients with inflammatory arthritis[14], or in diabetes[15]. It is important to recognize that these tests do not differentiate between latent infection and active TB disease, and should not be used as a primary test to diagnose active TB disease[16]. Another important awareness about IGRAs is that the IFN-γ response may change on serial testing, making interpretation difficult. In a systemic review of studies on healthcare workers underwent serial IGRA testing in low and intermediate TB incidence countries, reversion rates were found to be twice as much as conversion rates[17]. Most of these inconsistency occurred in subjects in whom their baseline results were near diagnostic threshold. Within-subject variability was also shown to be considerable across all studies. This raises questions on the reliability of existing laboratory ranges and cut-off values. Nevertheless, the IGRAs data are generally promising and most TB guidelines have now incorporated IGRAs as part of TB work-up. In a survey of 33 practice guidelines and position papers from 25 countries and 2 supranational organizations, Denkinger CM *et al* showed that the approaches are highly diversified on the use of IGRAs[18]. The four common approaches are (1) a two-step approach of TST first, followed by IGRA either when the TST is negative (to increase sensitivity, mainly in immunocompromised subjects), or when the TST is positive (to increase specificity, mainly in BCG-vaccinated individuals); (2) Either TST or IGRA, but not both; (3) IGRA and TST together (to increase sensitivity) and (4) IGRA only, replacing the TST. A systemic review from five low-to-medium TB-burden countries seem to suggest a lower cost whichever way IGRAs are used[19]. Taken together, IGRAs are increasingly being utilized, well-received and appear economically viable when used appropriately.

So, where do we go from here?

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One remaining consideration is whether large-scale LTBI screening of selected populations in already high TB burden countries has clear benefit. Most studies that support this policy stem from the perspectives of low-to-intermediate burden countries of mostly developed nations. This difference has the potential to alter the dynamics of TB transmission and reactivation in the community. Currently, Malaysia is categorized as intermediate burden by WHO [20] but some states like Sabah, Sarawak and Federal Territories had registered "high burden" notification (incidence) rates of over 100 per 100 000 population [21]. Implementing a national policy of screening and initiating preventive treatment in large high risk population like diabetes of a relatively high TB burden country like Malaysia would raise many serious questions. The proposal by Swarna Nantha to study the prevalence of LTBI, preferably with IGRAs, in Malaysian communities as a whole and specifically compare diabetic population with and without other comorbidities is appropriate. These studies need to be sufficiently large to be interpretable and their results will pave way for change in national TB policy if need be. Our current national primary health initiative to screen and treat non-communicable disease is commendable and may provide the opportunity to screen for LTBI in certain groups for preventive treatment if this exercise proves worthwhile. And the use of IGRAs should certainly be considered.

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