Effective Tuberculosis and Hepatitis Screening Prior to Anti-TNF- α Therapy: Are We There Yet?

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Anti-tumor necrosis factor- α (anti-TNF- α) drugs are widely used for the management of patients who suffer from Crohn's disease (CD) and ulcerative colitis (UC). Screening for latent tuberculosis infection (LTBI) and hepatitis B virus (HBV) is mandatory prior to commencing therapy with anti-TNF- α drugs, due to an increased reactivation risk for these diseases. Unfortunately, in the case of LTBI, a consensus has not been reached, highlighted by the heterogeneity of current guidelines, regarding the use of the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) as parts of the initial screening strategy [1, 2].

Historically, the diagnosis of LTBI has been dependent on the TST whose mechanism relies on a delayed-type T cell mediated hypersensitivity reaction to purified protein derivative (PPD). Regrettably, the TST has well-known limitations including potential sources for false positive results, due to the non-specific nature of PPD leading to cross-reactivity with non-tuberculosis mycobacterium and individuals who have received bacillus Calmette-Guérin vaccination. Moreover, there is intrinsic test subjectivity due to induration interpretation; furthermore, two health-care visits are required. Alternatively, the IGRAs, which measure the release of interferon-gamma post antigen exposure, have recently gained popularity as an alternative for LTBI diagnosis as their antigens are more specific for *Mycobacterium tuberculosis*. Nonetheless, IGRA testing is more expensive and requires appropriate infrastructure, potentially limiting its universal implementation.

In this issue, van der Have et al. [3] describe a cost-effectiveness analysis in patients with CD of screening strategies for LTBI and HBV: (1) traditional LTBI screening (TST and chest X-ray) versus additional IGRA testing; and (2) HBV screening versus no HBV screening. Neither extensive LTBI screening (traditional testing plus IGRA) nor HBV screening were cost-effective. Nevertheless, if LTBI prevalence was $>12\%$ or the TST false positivity rate $>20\%$, cost-effectiveness of extensive testing was achieved, emphasizing the importance of the varying global prevalence of LTBI and the sensitivity and specificity of LTBI diagnostic tests. Similarly, if HBV reactivity or HBV-related mortality were $>37\%$ and $>62\%$, respectively, HBV screening was cost-effective, leading the authors to conclude that although extensive LTBI screening and HBV screening are effective, their implementation should be targeted towards high-risk populations.

An interesting aspect to this study was how the authors calculated probabilities for the LTBI-component of the model, which appear to be largely derived from a recent meta-analysis which analyzed TST and IGRA performance in patients with inflammatory bowel disease (IBD) [4]. Concerning the perceived false-positivity rate of TST, it appears the authors based this off an estimate of discordance between TST+/IGRA– results, which is simply the discrepancy between these two tests in a patient. IGRAs are not commonly regarded as the 'gold standard' in LTBI diagnostics; therefore, the discordance is potentially an inaccurate quantification of false positivity. Moreover, it was unclear how the authors established the advantage that additional IGRA testing would have over traditional LTBI screening. It appears that they may have estimated this from the alternate discordant scenario TST–/IGRA+, which would lend itself to the same limitations as the false positivity risk.

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The issues above highlight a number of important barriers in the evaluation of LTBI diagnostics. The assessment of superiority in LTBI diagnostics has traditionally been limited due to a lack of a “gold standard” facilitating the quantification of sensitivity. Previous research has tried to circumvent this issue by quantifying this parameter by alternative methods, whether by utilizing active tuberculosis as a surrogate population [5] or by complex mathematical modeling [6]. Yet, these methods do have their drawbacks. Concerns have been raised about the use of active TB as a surrogate population for assessing LTBI diagnostic performance as the immune response is likely different between active TB and LTBI, therefore potentially impairing the validity of these estimates. Regarding the latter method of quantification, this study was a meta-analysis that openly addressed the limitations of their study including prominent heterogeneity between studies and limited data concerning TSPOT.TB (a type of IGRA). Furthermore, in the setting of IBD, this issue has been compounded by the contrast in geographic distribution between IBD and tuberculosis, since historically IBD afflicts populations living in more industrialized countries whereas tuberculosis is more of a burden to developing nations. Therefore, being able to reach a high enough number of active tuberculosis cases necessary to quantify the test sensitivity in IBD populations has been difficult. Moreover, the multiple factors complicating study design,

such as stratification based on tuberculosis risk factors, bacillus Calmette-Guérin vaccination status, severity of immunosuppression, and timing of screening make for a very arduous task.

Nonetheless, changes in the epidemiology of IBD are bringing new hope to the evaluation of this complex topic [7, 8]. While IBD remains prevalent in many developed nations, the incidence is increasing in many geographic areas such as South America, the Mediterranean, the Middle East, South Africa and South Asia. In conjunction, there remains a significant burden of tuberculosis in North America and other developed countries (Fig. 1) [9]. Global shifts are blurring the geographical distinctions between IBD and LTBI, which in turn may facilitate the quantification of outcomes such as LTBI sensitivity, which are reliant on the number of active tuberculosis cases in the test population. Moreover, this may enable the assessment of the benefit of LTBI screening prior to starting *any* immunosuppressive therapy versus screening prior to starting anti-TNF- α therapy only, as is currently recommended. The importance of this relates to the now established impairment of immunosuppression on the performance of the TST and the IGRA [4, 10]; this may help to explain the lack of cost-effectiveness of additional IGRA testing.

Since universal HBV screening was reported as not cost-effective, it is much more controversial to consider abolishing universal HBV screening rather than optimizing the

Fig. 1 Estimated TB incidence rates, 2011. Copyright © 2012. World Health Organization. Adapted with permission from the World Health Organization. Global Tuberculosis Report 2012, p. 13. Available from: http://www.who.int/tb/publications/global_report/en/

current approach, as in the case of LTBI screening. Prospective evaluation of universal screening versus screening of high-risk cases only is needed before modifying current screening recommendations. The question of restricting screening solely to high-risk individuals emphasizes the dual responsibilities of physicians as advocates of our patients, with support of mass screening, and also as stewards of the health care system, with a responsibility for optimizing the efficiency of health care on all fronts within the current economic climate.

In summary, this is a timely study that highlights the historical limitations of LTBI diagnostics in the context of the deficiencies of our current screening strategies. Through the epidemiological evolution of IBD, pertinent studies on this topic will become more feasible. Nevertheless, whichever method of screening is chosen, whether it be the TST, an IGRA or both, taking into consideration risk factors on a case by case basis is key; this will optimize the risk/benefit of the therapies currently available for the management of IBD.

References

1. Rahier JF, Ben-Horin S, Chowers Y, et al. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*. 2009;3:47–91.
2. Kucharz EJ, Korzeniewska-Kosela M, Kotulska A. Recommendations for prophylaxis and management of tuberculosis in patients treated with TNF-alpha antagonists. *Reumatologia*. 2008;46:51–54.
3. Van der Have M, Oldenburg B, Fidder HH, et al. Optimizing screening for tuberculosis and hepatitis B prior to starting tumor necrosis factor-alpha inhibitors in Crohn's disease. *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-013-2820-9.
4. Shahidi N, Fu YTN, Qian H, Bressler B. Performance of interferon-gamma release assays in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2012;18:2034–2042.
5. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med*. 2008;149:177–184.
6. Sadatsafavi M, Shahidi N, Marra F, et al. A statistical method was used for the meta-analysis of tests for latent TB in the absence of a gold standard, combining random-effect and latent-class methods to estimate test accuracy. *J Clin Epidemiol*. 2010;63:257–269.
7. Almadi MA, Ghosh S, Aljebreen AM. Differentiating intestinal tuberculosis from Crohn's disease: a diagnostic challenge. *Am J Gastroenterol*. 2009;104:1003–1012.
8. Molodecky NA, Shian Soon I, Rabi DM, Ghali WA, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46–54.
9. World Health Organization. Global tuberculosis report 2012. p. 13 Available from: http://www.who.int/tb/publications/global_report/en/. Accessed July 2013.
10. Cattamanchi A, Smith S, Steingart KR, et al. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2011;56:230–238.