

Beyond tumour necrosis factor inhibition: Revisiting latent tuberculosis infection testing in rheumatology

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Dear Editor,

Tuberculosis (TB) remains a major public health challenge in Asia and continues to require consideration during clinical decision-making in Singapore. Although the incidence of active TB in Singapore has declined, latent tuberculosis infection (LTBI) remains common, affecting an estimated 5–10% of the population and up to 30% of older adults.¹ For most individuals exposed to *Mycobacterium tuberculosis*, the pathogen persists in a dormant state with immune-mediated containment preventing progression to active disease. However, the lifetime risk of reactivation—estimated at 5–10%—is substantially increased by immune compromise, whether related to ageing, comorbidity, or iatrogenic immunosuppression.¹ This risk has had significant implications for rheumatology practice, where immune-modulating therapies are now central to the management of many immune-inflammatory rheumatic diseases. An increased risk of TB was identified soon after introduction of tumour necrosis factor inhibitors (TNFi), which led to the widespread adoption of LTBI screening prior to TNFi initiation, a practice now firmly embedded in international guidelines and clinical workflows.^{2,3} As the therapeutic landscape has expanded to include multiple non-TNFi biologics, targeted synthetic disease-modifying antirheumatic drugs such as Janus kinase inhibitors, and other immunosuppressive agents, clinicians may have extrapolated this approach beyond TNFi. While such caution is understandable in TB-endemic settings, indiscriminate screening may impose unnecessary costs, delay effective treatment and expose patients to LTBI therapy where benefit may be negligible. The uncertainty surrounding appropriate LTBI screening for non-TNFi therapies is addressed in the consensus statement in this issue, which provides evidence-informed recommendations for contemporary rheumatology practice in Singapore.

The approach taken to address LTBI by the Singapore Chapter of Rheumatology is systematic and clinically pragmatic, providing recommendations

that support informed decision-making in the clinic and at the bedside.⁴ Drawing on a comprehensive systematic literature review addressing the use of interferon-gamma release assay before initiation of number of non-TNFi agents and routine repeated testing for patients on TNFi who have previously tested negative for LTBI, the group applied the GRADE framework to assess the quality of evidence and strength of recommendations. Recommendations were crafted informed through multidisciplinary expert discussion and consensus voting. This methodological approach is well suited to areas where the evidence base is limited, heterogeneous, or indirect.⁵ The inclusion of experienced rheumatologists, together with an infectious disease and respiratory physician with expertise in TB, strengthens the credibility and relevance of the guidance. The consensus conditionally supports LTBI screening with interferon-gamma release assay prior to initiation of tocilizumab, Janus kinase inhibitors and moderate-to-high-dose glucocorticoids, while recommending against routine testing before cyclophosphamide. Importantly, the group also conditionally recommends against routine annual re-testing for LTBI in patients receiving TNFi who have had an initial negative screen, justified by low rates of reactivation in Singapore and a declining background TB incidence. This does not diminish the importance of clinical vigilance: ongoing assessment for TB symptoms and new exposure should remain part of routine care in TB-endemic settings. The restraint demonstrated in these recommendations—recommending careful clinical assessment over indiscriminate testing—represents a key strength of the consensus approach and distinguishes it from more prescriptive approaches.

While firm recommendations are often more satisfying to clinicians, the absence of high-quality evidence in this area necessitates caution. Conditional recommendations are an appropriate response to low-certainty evidence and should not be considered indecisive or lacking authority.⁶ Rather, they explicitly acknowledge uncertainty. In practice, such

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recommendations encourage clinicians to engage patients in informed discussions about the potential benefits and limitations of testing, incorporating individual values, preferences and tolerance for risk. A patient with high concern about TB and low risk tolerance may reasonably favour LTBI testing even when the expected yield is low, particularly if treatment decisions can be made without undue delay. Similarly, clinician judgement remains essential, as factors such as advanced age, frailty, cumulative or combination immunosuppression, and exposure risks may justify screening in selected cases. Conditional recommendations are therefore valuable in discouraging unnecessary testing for the majority, while preserving flexibility for individualised decision-making.

This consensus document has clear practical utility for day-to-day rheumatology care in Singapore. By discouraging LTBI testing where benefit is unlikely, the recommendations can reduce unnecessary delays in initiating effective therapy and avoid treatment of detected LTBI when the actual risk of reactivation with the chosen therapy is low. Given the potential toxicity of LTBI treatment, including hepatotoxicity and drug–drug interactions, this more targeted approach may reduce patient burden, healthcare costs and avoidable harm. It may also help streamline increasingly complex treatment pathways for patients with active inflammatory disease requiring escalation of therapy. Although developed within the Singapore context, the synthesis of evidence and guidance is likely to be relevant to clinicians practising in other settings with similar TB epidemiology. More broadly, the recommendations underscore the importance of clinicians always remaining cognisant of background rates of latent and active TB in their populations. In an increasingly globalised world, this includes consideration of TB risk in migrants originating from countries with higher LTBI prevalence, even when practising in high-income settings with lower overall TB incidence.

While these recommendations reflect the current available evidence, the question of LTBI screening will require periodic re-evaluation as therapeutics and epidemiology evolve. As new classes of immunomodulatory therapies emerge, clinicians will need to consider the implications for TB reactivation, informed by mechanism of action and likely effects on granuloma integrity. Future clinical trials should report TB-related exclusions and baseline LTBI screening clearly and should also be complemented by post-marketing evaluation. Over time, declining TB infections and changing LTBI prevalence—particularly as cohorts with lower lifetime exposure

age—may further alter the balance of benefit and harm associated with routine testing. Population-based pharmacovigilance and epidemiological studies, including international collaborations across TB-endemic and non-endemic regions will become increasingly important. Recommendations on LTBI risk assessment will require updating as evidence evolves. Given that TB remains a major global public health threat and that drug resistance poses an ongoing challenge, clinicians, researchers and policymakers share a responsibility to minimise unnecessary antimicrobial exposure while preventing active disease. Thoughtful, proportionate approaches to LTBI screening represent an important contribution to that goal.

Ethics statement

Not applicable.

Declaration

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