MAY 2025

CONSENSUS STATEMENT

Consensus Statement on Testing for Latent Tuberculosis

IN PEOPLE WITH RHEUMATIC DISEASE

CHAPTER OF RHEUMATOLOGISTS
COLLEGE OF PHYSICIANS, SINGAPORE

ACADEMY OF MEDICINE SINGAPORE

CHAPTER OF RHEUMATOLOGISTS
COLLEGE OF PHYSICIANS, SINGAPORE

EXECUTIVE SUMMARY OF RECOMMENDATIONS

Overarching principles

1. Screening, testing and management of patients with latent TB infection (LTBI) should be aligned with prevailing national policy.
2. The prevalence of TB differs across countries and should be considered when deciding whether to screen for LTBI prior to initiation of immunosuppressive therapy.
3. Screening for LTBI should be undertaken where it is reasonably feasible, taking into consideration the urgency of treatment.

Recommendations

In people with rheumatic diseases (PRD),

Recommendations	Grading of Recommendations Assessment, Development and Evaluation (GRADE)
1. We recommend that screening for LTBI with an interferon-gamma release assay (IGRA) should be performed prior to starting an interleukin 6 receptor blocker (e.g., tocilizumab).	Conditional
2. We recommend that screening for LTBI with an IGRA should be performed prior to starting Janus kinase inhibitors, e.g., tofacitinib, baricitinib, upadacitinib and filgotinib.	Conditional
3. We recommend that screening for LTBI with an IGRA should be performed prior to starting moderate to high dose glucocorticoids (prednisolone equivalent of ≥15mg/day for ≥8 weeks).	Conditional
4. We recommend that screening for LTBI with an IGRA need not be performed routinely prior to starting cyclophosphamide.	Conditional
5. We recommend that repeat testing for LTBI with an IGRA need not be performed routinely in PRD on tumour necrosis factor-alpha inhibitors (TNF-I), if initial testing is negative.	Conditional

BACKGROUND

TB, caused by the Mycobacterium tuberculosis complex, is endemic in Singapore. LTBI has a prevalence of 12.7% amongst Singapore residents,[1] with rates of up to 30% in older age groups.[2] Studies have consistently shown that people with rheumatic diseases with LTBI receiving TNF-I have higher risk of developing active TB compared with healthy controls, although the rates vary across studies.[3-5] Most international societies and expert groups therefore recommend screening and treating for LTBI prior to starting TNF-I, and we agree.[6-8] However, the evidence for screening and treating prior to treatment with non-TNF-I immunosuppressive agents, and the need for repeated screening in those on TNF-I, remains unclear. In this consensus statement, the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore sought to address questions regarding the need to screen for LTBI prior to treatment with non-TNF-I immunosuppressive agents (specifically non-TNF-I biologic disease-modifying antirheumatic drugs, targeted synthetic disease-modifying antirheumatic drugs, high dose glucocorticoids and cyclophosphamide).

TARGET AUDIENCE

Practicing rheumatologists involved in the care of PRD

METHODS

An expert panel was convened by the Chapter Chair and the Appraisal of Guidelines for Research & Evaluation framework[9] was used in the formulation of the statements. A core-working group reviewed the literature and formulated draft statements for rating by an invited task force panel, which included experts in adult Rheumatology, Infectious Diseases and Respiratory Medicine. A modified Delphi approach was used. Systematic literature reviews were performed to answer two research questions (see below). Where appropriate, in lieu of a systematic review of the primary literature, international best practice guidelines and recommendations of rheumatology societies on testing for LTBI in PRD were reviewed. Other academic bodies' recommendations for testing for LTBI in PRD and / or immunocompromising conditions were also considered. GRADE methodology[10] for assigning level of evidence and strength of recommendations was used.

GRADE system of assigning strength of recommendations:

- Strong: the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not.
- Conditional: the trade-offs are less certain - either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

PRD include, but are not limited to, those diagnosed with:

1. Chronic inflammatory arthritis (e.g. rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, juvenile idiopathic arthritis, adult-onset Still's disease)

2. Connective tissue diseases (e.g. systemic lupus erythematosus, immune mediated inflammatory myositis, Sjogren's syndrome, systemic sclerosis)
3. Primary systemic vasculitis
4. Autoinflammatory diseases

Research questions

1. Should PRD be tested for LTBI with an interferon-gamma release assay prior to starting the following non-TNF-I immunosuppressive agents?
    a. Anti-B-cell therapy (e.g.Rituximab)
    b. Anti-Interleukin 6 therapies (e.g. tocilizumab)
    c. Interleukin 17 inhibitors (e.g. secukinumab and ixekizumab)
    d. Interleukin 12/23 inhibitors (e.g. ustekinumab), and interleukin 23 inhibitors (e.g. guselkumab and risankizumab)
    e. CTLA4-Ig (e.g. Abatacept)
    f. Janus kinase inhibitors (e.g. tofacitinib, baricitinib, upadacitinib and filgotinib)
    g. Cyclophosphamide
    h. Moderate to high dose glucocorticoids, and if so, what is the threshold dose and duration of glucocorticoids?
2. For PRD on TNF-I who initially tested negative for LTBI, should annual repeat testing be done routinely?

RESULTS

Summary of literature

With regards to non-TNF-I immunosuppressive agents, most guidelines include generic statements when recommending testing for LTBI prior to starting targeted synthetic disease-modifying antirheumatic drugs[11,13,14,18,22] and biologics,[8,11,12,14,19] but do not make specific recommendations on the individual medications. The European Society of Clinical Microbiology and Infectious Diseases[22] and the Canadian Rheumatology Association[21] recommendations specify testing for LTBI prior to starting an anti-IL6 agent. The European Society of Clinical Microbiology and Infectious Diseases[22] and the Joint American Academy of Dermatology and National Psoriasis Foundation[15] guidelines specify screening for LTBI prior to the initiation of interleukin 17 inhibitors, interleukin 12/23 inhibitors and interleukin 23 inhibitors. The Canadian Rheumatology Association guidelines also specify testing for LTBI prior to starting abatacept.[21]

Most guidelines suggest that repeat testing for LTBI be done annually for patients on TNF-I who initially tested negative, especially if risk factors exist or develop over time and/or in countries where TB is endemic.[11,12,15,22]

Most guidelines recommend screening for LTBI for PRD who are likely to receive moderate to high dose glucocorticoids for a prolonged period of time.[11,16,17,19,20] There is variation in the dose

threshold and duration of glucocorticoid use, but most suggest a threshold daily dose of 15 mg or more of prednisolone equivalent for 4 or more weeks. No existing guideline includes a recommendation for cyclophosphamide.[8,11-20]

GLOSSARY

GRADE	Grading of Recommendations Assessment, Development and Evaluation
IGRA	Interferon-gamma release assay
LTBI	Latent TB infection
PRD	People with rheumatic diseases
TB	Tuberculosis
TNF-I	Tumour necrosis factor-alpha inhibitors

CHAPTER RECOMMENDATIONS

A detailed discussion of the recommendations and their underlying rationale is planned to be published in a peer reviewed journal. Meanwhile, a concise summary of the recommendations, for dissemination to practicing rheumatologists in Singapore, is provided below. We will review the recommendations again if or when more evidence in this area becomes available.

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Recommendations

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1. We recommend that screening for LTBI with an interferon-gamma release assay (IGRA) should be performed prior to starting an interleukin 6 receptor blocker (e.g. tocilizumab). *(Conditional)*
2. We recommend that screening for LTBI with an IGRA should be performed prior to starting Janus kinase inhibitors, e.g. tofacitinib, baricitinib, upadacitinib and filgotinib. *(Conditional)*
3. We recommend that screening for LTBI with an IGRA should be performed prior to starting moderate to high dose glucocorticoids (prednisolone equivalent of ≥15mg/day for ≥8 weeks). *(Conditional)*

4. We recommend that screening for LTBI with an IGRA need not be performed routinely prior to starting cyclophosphamide. *(Conditional)*
5. We recommend that repeat testing for LTBI with an IGRA need not be performed routinely in PRD on tumour necrosis factor-alpha inhibitors (TNF-I), if initial testing is negative. *(Conditional)*

There was no consensus reached for screening for LTBI prior to starting anti-B-cell therapy (e.g. rituximab), interleukin 17 inhibitors (e.g. secukinumab and ixekizumab), interleukin 12/23 inhibitors (e.g. ustekinumab), interleukin 23 inhibitors (e.g. guselkumab and risankizumab) and abatacept.

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