

Recommendations for screening for latent tuberculosis infection in people with rheumatic diseases: Consensus statement from the Singapore Chapter of Rheumatologists

Kar Mun Chong^{1,2} MRCP, Yi Wye Lai³ MRCP, Stanley Angkodjojo⁴ FAMS, Peter Pak Moon Cheung^{1,2} FRACP, Li-Ching Chew⁵ FRCP, Caroline Victoria Choong^{6,7} MBBS, Warren Fong⁵ MRCP, Li Yang Hsu⁸ MPH, Weng Giap Law⁹ FAMS, Mona Manghani³ FRACP, Amelia Santosa^{1,2} MRCP, Charlotte Su-Lin Tan^{1,2} FAMS, Teck Choon Tan⁹ FAMS, Gim Gee Teng^{1,10} MD, Manjari Lahiri^{1,2} MD

ABSTRACT

Introduction: Tuberculosis (TB) remains endemic in Asia, with latent TB infection (LTBI) being prevalent, especially among older adults. People with rheumatic diseases (PRD) who are treated with tumour necrosis factor-alpha inhibitors (TNF-I) are at increased risk of TB reactivation, prompting a strong recommendation for screening and treatment of LTBI prior to initiating TNF-I. However, the need for screening before starting non-TNF-I immunosuppressive agents remains unclear. This consensus statement from Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore, offers recommendations on LTBI screening before initiating non-TNF-I immunosuppressive agents, and the need for repeat LTBI testing in patients on TNF-I who initially tested negative.

Methods:: Systematic literature reviews were performed to evaluate published guidelines and recommendations for LTBI screening before starting non-TNF-I immunosuppressive agents, and the need for repeat testing for LTBI during TNF-I use. Recommendations were formulated based on the evidence and expert opinion according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results: The consensus comprises 3 overarching principles and 5 recommendations. We conditionally recommend that LTBI screening should be done before starting tocilizumab, Janus kinase inhibitors and moderate-to-high dose glucocorticoids. Conversely, routine screening need not be performed before starting cyclophosphamide. Annual testing for LTBI need not be performed routinely for patients on TNF-I if initial screening is negative.

Conclusion: These recommendations provide guidance for LTBI screening in PRD. All recommendations in this consensus are conditional, reflecting a lack of evidence or low-level evidence. These will be updated as new evidence emerges.

Keywords: immunosuppression, interferon-gamma release assay, latent tuberculosis infection, rheumatology, testing

CLINICAL IMPACT

What is New

- This is the first national consensus to address latent tuberculosis infection (LTBI) screening prior to initiation of non-tumour necrosis factor-alpha inhibitors (TNF-I) in patients with rheumatic diseases.
- It also clarifies the role of repeat LTBI testing in patients on TNF-I who initially tested negative.

Clinical Implications

- These recommendations will help clinicians make informed decisions on when to screen for LTBI, reducing variability in practice and avoiding unnecessary testing, while ensuring patient safety.
- These recommendations support more efficient use of healthcare resources and may inform institutional protocols and national policy in TB-endemic countries like Singapore.

The Annals is an open access journal, allowing non-commercial use under CC BY-NC-SA 4.0.

¹ Division of Rheumatology and Allergy, Department of Medicine, National University Hospital, Singapore

² Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

³ Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore

⁴ Rheumatology Unit, Department of General Medicine, Sengkang General Hospital, Singapore

⁵ Department of Rheumatology and Immunology, Singapore General Hospital, Singapore

⁶ Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore

⁷ National Tuberculosis Care Centre, Tan Tock Seng Hospital, Singapore

⁸ National University of Singapore Saw Swee Hock School of Public Health, Singapore

⁹ Elim Rheumatic Centre, Singapore

¹⁰ Division of Rheumatology, Department of Medicine, Alexandra Hospital, Singapore

Correspondence: A/Prof Manjari Lahiri, Division of Rheumatology and Allergy, Department of Medicine, National University Hospital, 1E Kent Ridge Road, Singapore 119228. Email: mdcml@nus.edu.sg

Acceptance: 17 December 2025

Published Online First: 31 December 2025

INTRODUCTION

Tuberculosis (TB), caused by the *Mycobacterium tuberculosis* complex, is endemic in Asia. Latent TB infection (LTBI) has a prevalence of 12.7% among Singapore residents,¹ with rates of up to 30% in older age groups.² Studies have consistently shown that people with rheumatic diseases (PRD) with LTBI receiving tumour necrosis factor- α inhibitors (TNF-I) have higher risk of developing active TB when compared with healthy controls, although the rates vary across studies.^{3–5} Hence, most international societies and expert groups recommend screening and treating for LTBI prior to starting TNF-I.^{6–8} However, the evidence for screening and treating prior to treatment with non-TNF-I immunosuppressive agents remains unclear. It is also uncertain whether there is a need for routine repeat (e.g. annual) testing in patients on TNF-I if they initially tested negative. In this consensus statement, the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore (henceforth called “the Chapter”), 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 (bDMARDs), targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), high-dose glucocorticoids and cyclophosphamide—as well as the need for routine repeat testing for patients on TNF-I who initially tested negative for LTBI.

METHODS

A core working group (CWG, comprising authors Manjari Lahiri, Kar Mun Chong and Yi Wye Lai) was formed to steer the consensus process. Members of the CWG formulated the research questions and performed a systematic literature review to answer them. The CWG developed draft recommendations for rating by an invited task force panel (TFP). A modified Delphi approach was used. The TFP comprised 10 Singapore-based, recognised adult rheumatologists from public and private healthcare institutions in Singapore, 1 infectious diseases specialist and 1 respiratory medicine specialist with a special interest in TB (i.e. authors Stanley Angkodjojo, Peter Pak Moon Cheung, Li-Ching Chew, Caroline Victoria Choong, Warren Fong, Li Yang Hsu, Weng Giap Law, Mona Manghani, Amelia Santosa, Charlotte Su-Lin Tan, Teck Choon Tan and Gim Gee Teng).

A conflict-of-interest declaration was required from all members of the CWG and TFP prior to the consensus process. Li Yang Hsu received honoraria from QIAGEN Singapore Pte Ltd for a speaking engagement. The other members declared no relevant conflicts of interest.

Literature review

Members of the CWG performed a systematic literature review to answer the following research questions (Fig. 1).

Fig. 1. Research questions.

1. Should people with rheumatic diseases (PRD) be tested for latent tuberculosis infection (LTBI) with an interferon-gamma release assay (IGRA) prior to starting the following non-tumour necrosis factor- α inhibitors (TNF-I) immunosuppressive agents?
 - a. Rituximab
 - b. Interleukin-6-receptor inhibitors (specifically tocilizumab)
 - c. Interleukin-17-inhibitors (specifically secukinumab and ixekizumab)
 - d. Interleukin-12/23-inhibitors (specifically ustekinumab), and interleukin 23 inhibitors (specifically guselkumab and risankizumab)
 - e. Abatacept
 - f. Janus kinase inhibitors (JAKi, specifically 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?

To review the evidence on LTBI screening in PRD, a systematic review of international best practice guidelines and recommendations from rheumatology, infectious disease, gastroenterology and dermatology societies were reviewed. The authors searched PubMed for publications between 2000 and 2024, using a combination of Medical Subject Headings (MeSH) terms and free text (“Latent Tuberculosis”[MeSH] OR “Tuberculosis”[MeSH] OR “Tuberculosis”) AND (“Immunosuppressive Agents”[MeSH] OR “Antirheumatic Agents”[MeSH] OR “Glucocorticoids”[MeSH] OR “Biologic” OR “DMARD”) AND (“Consensus” [MeSH] OR “Consensus Development Conference, NIH” [Publication Type] OR “Consensus Development Conference” [Publication Type] OR “Guidelines as Topic” [MeSH] OR “Practice Guidelines as Topic” [MeSH] OR “Guideline” [Publication Type] OR “Health Planning Guidelines” [MeSH] OR “Standard of Care” [MeSH] OR “Practice Guideline” [Publication Type] OR “Clinical Protocols” [MeSH]). Article types were limited to “Consensus Development Conference”, “Consensus Development Conference, NIH”, “Guideline” and “Practice Guideline”. The filters “English” (language) and “Humans” were also applied. This search yielded 40 citations. The authors screened through the titles and/or abstracts and excluded those that were duplicates or were outdated recommendations from the same body. They also did a manual search of primary licensing and other landmark drug clinical trials and registries.

Creation of draft statements

The CWG compiled findings from the literature review and formulated draft statements for rating by the TFP through an online survey platform. The Appraisal of Guidelines for Research & Evaluation (AGREE) framework⁹ was used in the formulation of the statements (see Supplementary Material Table S1), and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology¹⁰ was used for assigning level of evidence and strength of recommendations.

Rating of statements by the task force panel

Consensus was developed using a modified Delphi approach. The TFP was provided with a summary of evidence from the reviewed guidelines, trials and registries. For the first round of voting, the TFP was given a link to an online rating form and detailed instructions for rating via electronic mail. Based on the summarised evidence and their clinical expertise, the TFP independently rated each statement on a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). Consensus was achieved if there was at least 70% agreement (agree or strongly agree) or at least 70% disagreement (disagree or strongly disagree). The CWG and TFP then convened in a hybrid (in-person and online) synchronous meeting. One member of the CWG (Manjari Lahiri) moderated the proceedings. Results from the first round of rating were discussed and areas of uncertainties were clarified. Statements that did not reach consensus were reworded if necessary, and a second round of rating was carried out immediately via an online survey during the meeting. Results from the second round of voting were further discussed.

Finalising consensus statements

The final consensus statement was circulated to the TFP after the consensus meeting, and was approved by all members. Following this, the recommendations were reviewed by the College of Physicians, Singapore, Academy of Medicine Singapore, and the Ministry of Health, Singapore. Revisions were made, where appropriate, based on their input, prior to finalisation.

RESULTS

1. We conditionally recommend testing for LTBI with an IGRA in PRD prior to starting interleukin-6-receptor inhibitors e.g. tocilizumab, over not testing.

The level of evidence is low. The European Society of Clinical Microbiology and Infectious Diseases¹¹ and the Canadian Rheumatology Association guidelines¹² specifically recommend testing for LTBI prior to starting

tocilizumab. Most other guidelines^{8,13-16} include generic statements recommending testing for LTBI prior to starting biologics; however, they do not specifically mention tocilizumab. In the AMBITION trial¹⁷ studying the use of tocilizumab in patients with rheumatoid arthritis, patients were screened according to Singapore standards and were excluded if they had active TB or untreated LTBI. In the RADIATE trial,¹⁸ patients with active TB were excluded, but it was not mentioned if LTBI was screened for. In both studies, no opportunistic infections including TB were reported. In the GiACTA trial,¹⁹ it was not mentioned if LTBI testing was done and/or if patients with LTBI were excluded. The British Society for Rheumatology Biologics Register–Rheumatoid Arthritis registry²⁰ did not report any TB cases in the tocilizumab group. Very few cases were reported with tocilizumab use in the Hong Kong Society of Rheumatology Biologics Register.²¹ It was not mentioned if LTBI testing was done and/or if patients with LTBI were excluded.

This statement reached consensus on the first round of voting and was hence not discussed further.

2. We conditionally recommend testing for LTBI with an IGRA in PRD prior to starting JAKi, specifically tofacitinib, baricitinib, upadacitinib and filgotinib, over not testing.

The level of evidence is low. Most guidelines^{11,13,15,22} recommend that the same TB screening algorithm described for biologics should also be followed for patients receiving targeted synthetic disease-modifying antirheumatic drugs.

There is some evidence suggesting that use of JAKi may confer a higher risk for reactivation of LTBI. In clinical trials studying the use of JAKi in rheumatoid arthritis²³⁻²⁵ and psoriatic arthritis,²⁶ patients with active or untreated TB were excluded. In spite of this, a study with pooled data investigating the long-term safety of tofacitinib in the treatment of RA²³ reported 36 patients who developed active TB, 4 of whom had LTBI at screening and were appropriately treated. In another study with pooled data investigating the safety profile of baricitinib,²⁵ 10 patients were reported to have developed active TB. Very few cases of TB have been reported with tofacitinib use in registries.^{21,27,28} It was not mentioned if the patients in these registries had been screened or treated for LTBI prior to the initiation of tofacitinib.

This statement reached consensus on the first round of voting and was hence not discussed further.

3. We conditionally recommend testing for LTBI with an IGRA in PRD prior to starting moderate- to high-dose glucocorticoids (prednisolone equivalent of ≥ 15 mg/day for ≥ 8 weeks), over not testing.

The level of evidence is low. Most guidelines^{13,16,29,30,31} do recommend screening for LTBI for patients who are likely to receive moderate- to high-dose glucocorticoids for a prolonged period of time. There is variation in the dose and duration threshold recommended, but most^{13,30} suggest a threshold daily dose of ≥ 15 mg of prednisolone equivalent for ≥ 4 weeks. These recommendations arose from studies^{32,33} that compared patients on glucocorticoid dose of < 15 mg/day versus ≥ 15 mg/day. These 2 studies provided relevant observational data, but the level of evidence is low as 1 is a cohort study while the other is a case-control study.

Most cohort studies evaluating the incidence of TB and its risk factors showed that use of glucocorticoids was associated with increased risk of developing active TB,³³⁻³⁸ though the doses were not mentioned. It was also not mentioned if LTBI testing was done prior to initiation of glucocorticoids or whether patients with LTBI were excluded.

The TFP agreed that 15 mg/day of prednisolone equivalent is a reasonable dose as it is considered a moderate dose of glucocorticoids. However, in terms of duration, the TFP felt that a threshold duration of 8 weeks would be more pragmatic compared to 4 weeks. As almost all patients who require pulsed intravenous or high-dose oral glucocorticoids are expected to remain on high doses for at least 4 weeks—but may be able to taper the dose beyond 8 weeks—the higher threshold may reduce the burden of over testing. Given that it takes time for latent TB to reactivate, the TFP felt that 8 weeks is a reasonable threshold. Nevertheless, the decision should be individualised, especially if patients have epidemiological or clinical risk factors for latent TB (e.g. history of TB exposure, radiographic findings suggestive or previous or healed TB, residence in or travel from highly TB-endemic regions).

The TFP also acknowledged that in certain time-sensitive situations where patients require urgent treatment, it would not be feasible to delay initiation of glucocorticoids until after commencement of treatment of LTBI. Moreover, IGRA may yield false negative or indeterminate results in patients on high-dose glucocorticoids, and may hence warrant repeat or alternative modality testing subsequently if clinical suspicion remains. Given these limitations, this recommendation aims to serve as a reminder for physicians to minimally perform a risk assessment for patients who may require high-dose glucocorticoids, and monitor closely for reactivation of TB.

Finally, it was also mentioned that while there is insufficient evidence for TB reactivation while on other modes of administration of glucocorticoids, it may be reasonable to consider screening and treatment of

LTBI for PRD prescribed moderate- to high-dose glucocorticoids in all forms.

4. We conditionally recommend against routine testing for LTBI with an IGRA in PRD prior to starting cyclophosphamide.

The level of evidence is low. The European Alliance of Associations for Rheumatology¹³ suggests that a recommendation for cyclophosphamide cannot be made due to the low level of evidence. Most other guidelines^{8,11,12,14-16,22,29,31,39,40} are silent regarding LTBI testing prior to starting cyclophosphamide. Furthermore, most large clinical trials investigating the use of cyclophosphamide in ANCA-associated vasculitis⁴¹ and lupus nephritis^{42,43} did not report an increased risk of TB, though it was not mentioned whether LTBI testing was done or whether patients with LTBI were excluded.

Majority of the TFP disagreed with the statement during the first round of voting. A member of the TFP mentioned that screening for LTBI is also not routinely done in haematology patients on cyclophosphamide.

5. We conditionally recommend against routine repeat testing for LTBI with an IGRA in PRD on TNF-I, if initial testing is negative.

The optimal re-testing strategy for LTBI while on TNF-I therapy in those who initially tested negative remains to be established. While some guidelines are silent on repeat testing, others^{11,12,13,14,39} have suggested repeat testing if there are epidemiological risk factors, such as close contact with active TB cases, countries where TB is endemic, patients with selected underlying medical conditions. Regarding the recommended interval for repeat testing, 2 guidelines^{11,39} suggested annual repeat testing.

A member of the TFP reminded the group that the incidence of reactivated TB in Singapore is only 27 to 28 per 100,000 per year.² The rate of TB has been declining over the past 6 years.⁴⁴ Also, the cost of a single IGRA test in a public-sector hospital is about SGD200. Hence, routine repeat testing in a low-risk group of patients may lead to unnecessary cost with low yield.^{1,2} The TFP felt that instead, need for repeat testing should be individualised, guided by clinical signs and symptoms, known exposure to TB contacts and change in risk factors.

Rituximab

The level of evidence is low. Most guidelines^{8,13-16} include generic statements recommending testing for LTBI prior to starting biologics—but do not specifically mention rituximab. Evidence from small retrospective or observational data suggests that the risk of reactivation of TB with rituximab is low. In published

clinical trials studying the efficacy of rituximab in rheumatoid arthritis,^{45,46} ANCA-associated vasculitis⁴⁷ and lupus nephritis,⁴⁸ it is not mentioned if LTBI testing was done and/or if patients with LTBI were excluded. The REFLEX trial⁴⁶ specifically mentioned that there were no reported cases of TB over 24 weeks of the study. In biologics registries,^{20,21,27,28} very few cases of TB were observed in the rituximab group. Similarly, it was not mentioned if the patients in these registries had been screened or treated for LTBI prior to the initiation of rituximab.

This statement did not reach consensus. The TFP questioned the strength of evidence linking rituximab to an increased risk of TB reactivation. One member commented that the mechanism of action of rituximab primarily targets B cells, and is hence less implicated in TB reactivation compared to therapies affecting T-cell function. It was pointed out that testing for LTBI is also not routinely done in patients with haematological malignancies, where rituximab is commonly used, and no significant safety signals have emerged to date. Others took a more cautious stance, acknowledging that while the evidence is limited, isolated reports of TB reactivation do exist and warrant consideration. It was also pointed out that patients prescribed rituximab are often concurrently receiving other immunosuppressive therapies, including corticosteroids, which could contribute to a cumulative risk of TB reactivation.

Interleukin-17-I, specifically secukinumab and ixekizumab

The level of evidence is low. The Joint American Academy of Dermatology and National Psoriasis Foundation³⁹ and the European Society of Clinical Microbiology and Infectious Diseases guidelines¹¹ recommend screening for LTBI prior to the initiation of interleukin (IL)-17-I. Other guidelines vary in their assessment of risk. In a study pooling data from 21 randomised controlled trials investigating the long-term safety of secukinumab in patients with plaque psoriasis, psoriatic arthritis and ankylosing spondylitis,⁴⁹ it was mentioned that the patients enrolled in these trials were tested for LTBI, and could be included if LTBI treatment was started. No cases of TB reactivation were reported in these trials.

This statement did not reach consensus though the majority (66.7%) of the TFP agreed with testing for LTBI prior to starting IL-17-I on the first round of voting. Members of the TFP commented that the rates of TB may be low due to existing practices of screening and treating LTBI, rather than a truly low risk. They would still opt to treat LTBI in these patients and hence would test for LTBI prior to starting IL-17-I. Moreover, the drug inserts for Cozentyx (secukinumab; Novartis Pharmaceuticals Corp., NJ, USA) and Taltz (ixekizumab; Eli Lilly and Company, IN, USA)

recommend evaluating for TB prior to initiating treatment. It was suggested that from a practical standpoint, since patients considered for IL-17-I often have overlapping indications with TNF-I, LTBI screening would typically be conducted regardless, given the established need for testing prior to initiation of TNF-I. However, others felt that the evidence supporting treating LTBI in these cases is not strong and hence they would not offer screening. One member pointed out that real-world data⁵⁰ in the dermatology field has shown low reactivation rates among patients with LTBI who received IL-17-I. However, it is important to note that the majority of patients in this study received chemoprophylaxis after being screened for LTBI. Data specifically on patients with untreated LTBI who received IL-17-I are limited.

Interleukin-12/23-I, specifically ustekinumab, and Interleukin-23-I, specifically guselkumab and risankizumab

The level of evidence is low. The Joint American Academy of Dermatology and National Psoriasis Foundation³⁹ and the European Society of Clinical Microbiology and Infectious Diseases guidelines¹¹ recommend screening for LTBI prior to the initiation of IL-12/23-I. Other guidelines vary in their assessment of risk. In the PSUMMIT 2 trial⁵¹ investigating the efficacy and safety of ustekinumab in patients with psoriatic arthritis, patients with a history of active TB were excluded. Other patients were tested for LTBI and could be included if LTBI treatment was started. No cases of TB reactivation were reported through week 60. In the DISCOVER-1⁵² and DISCOVER-2 trials⁵³ of guselkumab in patients with psoriatic arthritis, patients with active TB were excluded. Other patients were tested for LTBI and could be included if they were on LTBI treatment. No cases of new-onset TB or reactivation of LTBI occurred through 1 year. Data regarding TB reactivation with IL-12/23-I and IL-23-I use from biologics registries are not yet available.

This statement did not reach consensus. The majority of the TFP concurred that these drugs are less commonly used in Rheumatology. One member remarked that he would test for LTBI in all patients with spondyloarthritis, given the potential need for TNF-I and the associated risk of TB reactivation.

Abatacept

The level of evidence is low. The Canadian Rheumatology Association guidelines¹² specifically recommend testing for LTBI prior to starting abatacept. Most other guidelines^{8,13-16} include generic statements recommending testing for LTBI prior to starting biologics; however, they do not specifically mention abatacept. In biologics registries,^{20,27,28} very few cases of TB were reported with abatacept use. Again, it

was not mentioned if the patients in these registries had been screened or treated for LTBI prior to the initiation of abatacept.

This statement did not reach consensus though the majority (66.7%) of the TFP agreed with testing for LTBI prior to starting abatacept on the second round of voting. The TFP noted that this drug is not commonly used in Singapore.

DISCUSSION

This consensus recommendation provides guidance to healthcare providers regarding screening for LTBI prior to treatment with non-TNF- α immunosuppressive agents (specifically non-TNF- α bDMARDs, tsDMARDs, moderate- to high-dose glucocorticoids and cyclophosphamide), as well as regarding routine

repeat testing for patients on TNF- α who initially tested negative for LTBI. This recommendation is based on an updated literature review, evidence synthesis using the GRADE methodology, and a modified Delphi consensus method. Ten adult rheumatologists, 1 infectious diseases specialist and 1 respiratory medicine specialist with a special interest in TB were convened for this work, which is representative of the healthcare providers for PRD in Singapore. The updated evidence and consensus are intended to help guide decision making for screening and treatment for LTBI prior to starting non-TNF- α immunosuppressive agents, and to remind physicians of nuances to consider for repeat testing for LTBI in patients on TNF- α .

The consensus recommendation achieved strong agreement for screening and treating for LTBI prior

Table 1. Voting results.

No.	Recommendations	Round 1		Round 2	
Reached consensus: Agreement		% agreement	% disagreement	% agreement	% disagreement
1	We recommend that people with rheumatic diseases (PRD) should be tested for latent tuberculosis infection (LTBI) with an interferon-gamma release assay (IGRA) prior to starting interleukin 6 receptor inhibitors, e.g. tocilizumab.	75	8.3	NA	NA
2	We recommend that PRD should be tested for LTBI with an IGRA prior to starting Janus kinase inhibitors (JAKi), specifically tofacitinib, baricitinib, upadacitinib and filgotinib.	83.4	0	NA	NA
3	We recommend that PRD should be tested for LTBI with an IGRA prior to starting moderate- to high-dose glucocorticoids (prednisolone equivalent of ≥15 mg/day for ≥4 weeks). The duration was revised from 4 weeks to 8 weeks before the second round of voting.	66.6	25	75	8.3
Reached consensus: Disagreement		% agreement	% disagreement	% agreement	% disagreement
4	We recommend that PRD should be tested for LTBI with an IGRA prior to starting cyclophosphamide. There was no change in wording for the second round of voting.	25	58.3	8.3	91.7
5	We recommend that testing for LTBI with an IGRA be repeated annually in PRD on tumour necrosis factor-alpha inhibitors (TNF-I), if initial testing is negative. There was no change in wording for the second round of voting.	41.6	41.7	8.3	91.7
Did not reach consensus		% agreement	% disagreement	% agreement	% disagreement
6	Rituximab	33.3	41.6	25	66.7
7	Interleukin-17-inhibitors (IL-17-I), specifically secukinumab and ixekizumab	66.7	16.7	41.7	33.3
8	Interleukin-12/23 inhibitors (IL-12/23-I), specifically ustekinumab, and interleukin 23 inhibitors (IL 23-I), specifically guselkumab and risankizumab	50	33.3	41.7	33.3
9	Abatacept	58.3	25	66.7	16.7

IGRA: interferon gamma release assay; JAKi: Janus kinase inhibitors; LTBI: latent tuberculosis infection; PRD: people with rheumatic diseases; TNF- α : tumour necrosis factor- α inhibitors

Table 2. Summary of recommendations.

Recommendations	
1.	We conditionally recommend testing for latent tuberculosis infection (LTBI) with an interferon-gamma release assay (IGRA) in people with rheumatic diseases (PRD) prior to starting interleukin 6 receptor inhibitors, e.g. tocilizumab, over not testing.
2.	We conditionally recommend testing for LTBI with an IGRA in PRD prior to starting Janus kinase inhibitors, specifically tofacitinib, baricitinib, upadacitinib and filgotinib, over not testing.
3.	We conditionally recommend testing for LTBI with an IGRA in PRD prior to starting moderate- to high-dose glucocorticoids (prednisolone equivalent of ≥ 15 mg/day for ≥ 8 weeks) over not testing.
4.	We conditionally recommend against routine testing for LTBI with an IGRA in PRD prior to starting cyclophosphamide.
5.	We conditionally recommend against routine repeat testing for LTBI with an IGRA in PRD on tumour necrosis factor- α inhibitors (TNF-I), if initial testing is negative.

to initiating tocilizumab and JAKi, consistent with recommendations from existing guidelines^{11,12} and real-world evidence of elevated risk of TB reactivation.^{23,25} These recommendations are further supported by the known mechanistic effects of these agents, particularly their disruption of T-cell-mediated immunity, a critical defence against latent TB reactivation.⁵⁴ JAKi block the JAK-STAT signalling pathway, that is critical for cytokine signalling, including interferon-gamma (IFN- γ) which is essential for macrophage activation and control of latent TB. Emerging evidence also suggests additional alteration of regulatory T-cell function, further compromising TB containment.⁵⁵⁻⁵⁷ However, it should be cautioned that delaying initiation of tocilizumab or JAKi while treating LTBI should be balanced against the clinical need for disease control.

Conversely, the majority of the TFP concurred that screening for LTBI need not be done routinely prior to starting cyclophosphamide. For glucocorticoids, the panel endorsed screening for LTBI prior to starting moderate- to high-dose glucocorticoids, defined by the panel as prednisolone equivalent of ≥ 15 mg/day for ≥ 8 weeks. This balances the risk of LTBI reactivation against clinical feasibility in acute settings. The TFP also agreed that repeat testing for LTBI while on TNF-I need not be routinely done in view of Singapore's declining TB rates,⁴⁴ favouring a case-based approach instead, to best optimise resource use. Despite broad consensus on several recommendations, we acknowledge that none achieved unanimous agreement or disagreement. This reflects the paucity of high-level evidence specifically addressing LTBI screening strategies, as much of the current guidance is extra-

polated from observational data and indirect evidence, as well as expert opinion. Prospective studies, ideally randomised controlled trials, or large registry-based cohort studies, that evaluate TB reactivation outcomes under varying screening protocols, are required to strengthen future recommendations. Another limitation is that our recommendations did not consider the cost impact on society or individuals.

In summary, we have synthesised an updated literature review and formulated consensus recommendations on the need for screening for LTBI prior to treatment with non-TNF-I immunosuppressive agents in PRD. This work represents a systematic effort by the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore. Recommendations for the individual patient need to take into account the patient's clinical condition and risk factors for TB, values, preferences and accessibility to testing for LTBI. These recommendations will undoubtedly evolve as new evidence becomes available.

Supplementary material

Table S1. AGREE reporting checklist.

Acknowledgements

The authors thank the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore, for providing funding and logistical support for the consensus meeting.

Ethics statement

Not applicable. No ethics approval was required as this manuscript is a consensus statement based solely on literature review and Delphi consensus process, with no involvement of human subjects or patient data.

Declaration

Li Yang Hsu received honoraria from QIAGEN Singapore Pte Ltd for a speaking engagement. The remaining authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

REFERENCES

1. Yap P, Tan KHX, Lim WY, et al. Prevalence of and risk factors associated with latent tuberculosis in Singapore: A cross-sectional survey. *Int J Infect Dis* 2018;72:55-62.
2. Ministry of Health, Singapore. Update on Tuberculosis Situation in Singapore. Ministry of Health Singapore. Published 23 March 2025. <https://www.moh.gov.sg/newsroom/update-on-tuberculosis-situation-in-singapore-2025>. Accessed 4 May 2025.
3. Askling J, Forede CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum* 2005; 52:1986-92.

4. Gómez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003; 48:2122-7.
5. Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum* 2004;50:372-9.
6. Guidelines on the Management of Latent Tuberculosis Infection. Geneva: World Health Organization; 2015.
7. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax* 2005;60:800-5.
8. Holroyd CR, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis-Executive summary. *Rheumatology (Oxford)* 2019;58:220-6. Erratum in: *Rheumatology (Oxford)*. 2019;58:372.
9. Brouwers MC, Browman GP, Burgers JS, et al. Appraisal of Guidelines for Research & Evaluation II (AGREE II) Instrument. The AGREE Next Steps Consortium. May 2009.
10. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.
11. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbial Infect* 2018 ;24:S21-S40.
12. Bombardier C, Hazlewood GS, Akhavan P, et al. Canadian Rheumatology Association. Canadian Rheumatology Association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: part II safety. *J Rheumatol* 2012;39:1583-1602.
13. Fragoulis GE, Nikiphorou E, Dey M, et al. 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2023;82:742-53.
14. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheum* 2016;68:1-26.
15. Screening for Latent Tuberculosis Infection (LTBI) and its management in inflammatory arthritis patients. Australian Rheumatology Association. December 2022.
16. Lichauco JJT, Tankeh-Torres SA, Navarra SV, et al. Philippine guidelines on the screening for tuberculosis prior to the use of biologic agents. *APLAR J Rheumatol* 2006;9:184-92.
17. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010;69:88-96.
18. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologics: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67:1516-23. Erratum in: *Ann Rheum Dis* 2009;68:296.
19. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med* 2017;377:317-28.
20. Lauper K, Kearsley-Fleet L, Galloway JB, et al. Evaluation of serious infections, including Mycobacterium tuberculosis, during treatment with biologic disease-modifying anti-rheumatic drugs: does line of therapy matter? *Rheumatology (Oxford)* 2024;63:1957-64.
21. O'Young CKY, Ho KM, So H, et al. Recommendations on management of latent tuberculosis infection in patients initiating anti-tumour necrosis factor biologics. *J Clin Rheumatol and Immunol* 2021;21:1-7.
22. Lau CS, Chia F, Dans L, et al. 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. *Int J Rheum Dis* 2019;22:357-75.
23. Cohen SB, Tanaka Y, Mariette X, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann Rheum Dis* 2017;76:1253-62.
24. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. *Arthritis Rheumatol* 2019;71:1788-800.
25. Smolen JS, Genovese MC, Takeuchi T, et al. Safety Profile of Baricitinib in Patients with Active Rheumatoid Arthritis with over 2 Years Median Time in Treatment. *J Rheumatol* 2019;46:7-18. Erratum in: *J Rheumatol* 2019;46:1648-9.
26. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. *N Engl J Med* 2017;377:1525-36.
27. Kremer JM, Bingham CO 3rd, Cappelli LC, et al. Postapproval Comparative Safety Study of Tofacitinib and Biological Disease-Modifying Antirheumatic Drugs: 5-Year Results from a United States-Based Rheumatoid Arthritis Registry. *ACR Open Rheumatol* 2021;3:173-84.
28. Simon TA, Suissa S, Skovron ML, et al. Infection outcomes in patients with rheumatoid arthritis treated with abatacept and other disease-modifying antirheumatic drugs: Results from a 10-year international post-marketing study. *Semin Arthritis Rheum* 2024;64:152313.
29. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018 Apr;113(4):481-517. Epub 2018 Mar 27. Erratum in: *Am J Gastroenterol* 2018;113:1101.
30. Internal Clinical Guidelines Team (UK). Tuberculosis: Prevention, Diagnosis, Management and Service Organisation. London: National Institute for Health and Care Excellence (UK); 2016.
31. Ang MLT, Chan SM, Cheng LT, et al. Singapore tuberculosis (TB) clinical management guidelines 2024: A modified Delphi adaptation of international guidelines for drug-susceptible TB infection and pulmonary disease. *Ann Acad Med Singap* 2024;53:170-86.
32. Long W, Cai F, Wang X, et al. High risk of activation of latent tuberculosis infection in rheumatic disease patients. *Infect Dis (Lond)* 2020;52:80-6.
33. Jick SS, Lieberman ES, Rahman MU, et al. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum* 2006;55:19-26.
34. Wu PH, Lin YT, Yang YH, et al. The increased risk of active tuberculosis disease in patients with dermatomyositis - a nationwide retrospective cohort study. *Sci Rep* 2015;5:16303.
35. Zhang L, Zou X, Jiang N, et al. Incidence and risk factors of tuberculosis in systemic lupus erythematosus patients: a multi-center prospective cohort study. *Front Immunol* 2023;14:1157157.
36. Wu Q, Liu Y, Wang W, et al. Incidence and prevalence of tuberculosis in systemic lupus erythematosus patients: A systematic review and meta-analysis. *Front Immunol* 2022; 13:938406.
37. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. *Arthritis Rheum* 2009;61:300-4.
38. Lai CC, Lee MT, Lee SH, et al. Risk of incident active tuberculosis and use of corticosteroids. *Int J Tuberc Lung Dis* 2015;19:936-42.

39. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol* 2019;80:1029-72.
40. Lewinsohn DM, Leonard MK, LoBue PA, et al. ATS/CDC/IDSA Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis* 2017;64:e1-e33.
41. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009;150:670-80.
42. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;46:2121-31.
43. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009;20:1103-12.
44. The Straits Times. Local TB cases drop for sixth year straight in 2024. The Straits Times. 23 March 2024. <https://www.straitstimes.com/singapore/local-tb-cases-drop-for-sixth-year-straight-in-2024>. Accessed 4 May 2025.
45. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006;54:1390-400.
46. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54:2793-806.
47. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363:221-32.
48. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012;64:1215-26.
49. Deodhar A, Mease PJ, McInnes IB, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Res Ther* 2019;21:111.
50. Torres T, Chiricozzi A, Puig L, et al. Treatment of Psoriasis Patients with Latent Tuberculosis Using IL-17 and IL-23 Inhibitors: A Retrospective, Multinational, Multicentre Study. *Am J Clin Dermatol* 2024;25:333-42.
51. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014;73:990-9.
52. Deodhar A, Helliwell PS, Boehncke WH, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naïve or had previously received TNF α inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial *Lancet* 2020;395:1115-25. Erratum in: *Lancet* 2020;395:1114.
53. Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naïve patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2020;395:1126-36. Erratum in: *Lancet* 2020;395:1114.
54. Urdahl KB. Understanding and overcoming the barriers to T cell-mediated immunity against tuberculosis. *Semin Immunol* 2014;26:578-87.
55. Shanmuganathan G, Orujyan D, Narinyan W, et al. Role of Interferons in Mycobacterium tuberculosis Infection. *Clin Pract* 2022;12:788-96.
56. Kubo S, Nakayamada S, Sakata K, et al. Janus Kinase Inhibitor Baricitinib Modulates Human Innate and Adaptive Immune System. *Front Immunol* 2018;9:1510.
57. Ghoreschi K, Jesson MJ, Li X, et al. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J Immunol* 2011;186:4234-43.