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Recommendations on Management of Latent Tuberculosis Infection in Patients Initiating Anti-tumor Necrosis Factor Biologics

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ABSTRACT

Patients with immune-mediated inflammatory diseases on anti-tumor necrosis factor (TNF) agents are at increased risk of developing active tuberculosis (TB). Screening and treatment of latent tuberculosis infection (LTBI) with the use of a standard screening protocol is important in reducing the risk of TB reactivation during therapies with anti-TNF agents. The Latent Tuberculosis Infection Working Group under the Tuberculosis Control Coordinating Committee of the Department of Health and the Hospital Authority has reviewed and assessed local and international scientific evidence and formulated guideline statements on the management of LTBI in patients initiating anti-TNF biologics.

Keywords: Anti-tumor Necrosis Factor Agents; Active Tuberculosis; Latent Tuberculosis Infection.

INTRODUCTION

The use of biologics, in particular the anti-tumor necrosis factor (TNF) agents, is associated with an increased risk of tuberculosis (TB) activation in patients with rheumatic diseases, dermatologic diseases, and inflammatory bowel diseases [1–5]. Latent TB infection (LTBI) screening and treatment to prevent reactivation of TB is important before the initiation of biological therapies. Tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are the main screening tools of LTBI. The Hong Kong Society of Rheumatology has issued consensus statements on the screening of LTBI prior to the use of biological agents for rheumatic diseases in Hong Kong in 2015, which is an update of the recommendations published earlier in 2005 [6,7]. Upon the release of an updated and consolidated guidelines for programmatic management of LTBI by the World Health Organization (WHO) in 2018, a LTBI Working Group comprising local TB specialists and specialists from related specialties was set up under the TB Control Coordinating Committee of Department of Health (DH) and Hospital Authority (HA) [8]. The LTBI Working Group has reviewed and assessed local and international scientific evidence, and formulated recommendations on management of LTBI in patients initiating anti-TNF biologics. The recommendations

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have been further discussed and reviewed among members of the Hong Kong Society of Rheumatology. This article describes the TB risks among patients receiving anti-TNF biologics and summaries the rationale and the guideline statements made by the LTBI Working Group on screening and treatment of LTBI in patients initiating anti-TNF biologics. The newer targeted synthetic drugs are not covered by the guideline statements as the number of cases put on these newer drugs locally has remained small and data to inform the best screening strategy for this group is inadequate at present [4].

RISK OF TB IN PATIENTS WITH RHEUMATIC DISEASES INITIATING OR UNDERGOING ANTI-TNF THERAPY

With increasing use of biologic agents for management of immune-mediated inflammatory diseases, there are growing concerns regarding the increased rates of TB secondary to the disturbance of cytokine-mediated signaling by these therapies. An UK study showed the overall prevalence of LTBI in patients with inflammatory arthritis prescribed biologic therapy in an endemic area is 10% and this risk warrants careful screening and monitoring while adherence to strict screening protocol reduces the risk of active TB infection [1]. Among the different biologic agents, anti-TNF biologics are associated with a higher risk of TB activation in patients with rheumatic diseases [2]. In a U.S. study, the anti-TNF associated rates of TB was 49 (95% confidence interval [CI]: 18–79) per 100 000 person-years among anti-TNF users [3]. Among the 3765 patients from the Hong Kong Society of Rheumatology Biologics Registry, a total of 83 TB cases were reported as of May 2021, majority (90.4%) occurring in patients treated with anti-TNF biologics (Table 1) [4]. About half of the cases (43 cases) occurred in the first year of treatment. In a recent study that examined medical data of patients with immune-mediated inflammatory diseases treated with biologics from a territory-wide computerized database in Hong Kong, the overall standardized incidence ratio (SIR) of TB was 10.91 (95% CI: 8.00–13.82) compared with the general population. Patients treated with infliximab had a nearly 26 times increased risk of TB (SIR 25.95; 95% CI: 17.23–34.67) [5]. Screening and treatment of LTBI with the use of a standard screening protocol is therefore important in reducing the risk of TB reactivation during therapies with the anti-TNF agents.

Table 1. Biological/targeted disease-modifying antirheumatic drugs used among 83 tuberculosis patients from the Hong Kong Society of Rheumatology Biologics Registry (as of May 2021)* [4]

Agent used	Number of TB cases (%)
Infliximab	32 (38.6%)
Adalimumab	17 (20.5%)
Etanercept	14 (16.9%)
Golimumab	11 (13.3%)
Tocilizumab	3 (3.6%)
Tofacitinib	3 (3.6%)
Rituximab	1 (1.2%)
Remsima	1 (1.2%)
Baricitinib	1 (1.2%)
Total	83 (100%)

TB = tuberculosis

*The biological agents used according to the latest report as of May 2021 included: etanercept, adalimumab, golimumab, infliximab, tocilizumab, tofacitinib, rituximab, abatacept, certolizumab, secukinumab, baricitinib, remsima, ustekinumab, belimumab, sarilumab, ixekizumab, pamidronate, and truxima; duration of exposure to individual biologic not available.

Assessment of LTBI before anti-TNF treatment

Patients contemplating on anti-TNF therapy should have a detailed medical history and clinical examination, as well as a chest radiograph taken. Any patients who have an abnormal chest radiograph suspicious of TB or previous history of TB or TB treatment should be referred to a TB specialist for further evaluation. Based on the WHO recommendations, either TST or IGRA are acceptable for LTBI screening [9]. The traditional TST elicits a delayed-typed hypersensitivity reaction to an intradermal injection of purified protein derivative (PPD). A reaction may occur not only from Mycobacterium tuberculosis (MTB) infection, however, but also from Bacillus Calmette–Guerin (BCG) vaccination or infection with Mycobacteria other than tuberculosis (MOTT) as the antigens present in PPD are also present in MOTT and the Mycobacterium bovis BCG substrains. Moreover, TST may be rendered negative in immunocompromised subjects. There is evidence of low sensitivity of TST for detecting LTBI in patients using corticosteroids at doses greater than 20 mg for longer than 2 weeks [3]. The IGRA tests are more specific than TST, as the antigens used, ESAT-6 and CFP-10, are more MTB specific and absent from

BCG substrains and most MOTT species. A study that evaluated the agreement between the two tests in the diagnosis of LTBI among African patients with immune-mediated inflammatory diseases reported that IGRA was more specific than TST, and that the substitution of TST by IGRA led to a significant reduction in the need of LTBI treatment [10]. The agreement between the two test results was low, however, in that study. In a local study that evaluated the performance of TST vs IGRA, the level of agreement between the two tests improved from fair to moderate when the TST cut-off was lowered from 10 mm to 5 mm [11]. Given the generally low agreement between IGRA and TST, and that both tests have similar but poor ability to identify patients with LTBI at risk of developing active TB disease, the use of either TST or an IGRA for the investigation of LTBI is recommended. The usefulness of dual testing was evaluated in a local study that assessed 217 consecutive patients receiving biologic and targeted synthetic disease-modifying antirheumatic drugs for rheumatic diseases. TB occurred in nine patients in the single testing group and one patient in the dual testing group (7.4% vs 1.0%, $P = 0.045$) [12]. A dual testing strategy of TST and IGRA therefore appeared to be effective and may be considered especially in patients where the risk of progression to active TB disease is high, for example, those who are on systemic steroid therapy at the time of LTBI screening, or if infliximab therapy is anticipated, though confirmative data from further studies are needed. Given the limitations of the TST and IGRA and that both tests have a low positive predictive value (PPV) to predict progression from LTBI to active TB, new tests that may better predict TB disease to allow more targeted preventive treatment are needed.

The majority of potential recipients of anti-TNF therapy will have a normal chest radiograph. There are insufficient data to inform the best management strategy regarding patients with an abnormal chest radiograph consistent with past TB who have received previous adequate treatment. Some international guidelines recommended that anti-TNF treatment can be started but the patient should be monitored clinically every 3 months with a chest radiograph and sputum cultures if respiratory symptoms develop [13–15]. Patients with past TB who have inadequate TB treatment should have active TB excluded by appropriate investigations under the care of a TB specialist. LTBI treatment has been recommended for this category of patients even when tests for latent infection are negative, after exclusion of active TB [15].

Treatment of LTBI

Preventive treatment for LTBI has been shown to reduce TB risk by 65% (RR: 0.35, 95% CI: 0.15–0.82) [16]. A positive test result from either TST or IGRA (after exclusion of active TB) is an indication for LTBI treatment. LTBI treatment is also generally recommended for patients with old fibrotic lung shadows on chest radiographs after exclusion of active TB by appropriate sputum and/or other tests. For those requiring LTBI treatment, isoniazid given at a daily dose of 5 mg/kg (maximum 300 mg) for at least 6 to 9 months is generally recommended unless there are contra-indications. Pyridoxine at a daily dose of 10 mg is recommended in patients with human immunodeficiency virus (HIV) infection, alcohol dependency, malnutrition, diabetes mellitus, chronic liver disease, renal failure as well as pregnant women to prevent peripheral neuropathy when isoniazid is used. Isoniazid treatment for 9 months (9H) may be preferred to 6 months (6H) basing on the results of a re-analysis of studies by the U.S. Public Health Service, which suggested optimal effectiveness was achieved after 9 months [17]. On the other hand, the completion rate of 9H has been reported to be generally low. In one study that examined LTBI treatment acceptance and completion in the United States and Canada, only approximately half of all patients beginning 9H completed therapy [18]. Both 6H and 9H are considered suitable regimens for LTBI treatment. Alternative regimens may include rifampicin (given at a daily dose of 10 mg/kg (maximum 600 mg) plus isoniazid (given at a daily dose of 5 mg/kg (maximum 300 mg) for 3 months (3HR). In case the patient cannot tolerate isoniazid or if isoniazid resistance is anticipated, daily rifampicin for 4 months (4R) may be used. In a recent study that examined the relative performance of 4R vs 9H for treatment of LTBI, the 4R regimen was not inferior to 9H regimen for the prevention of active TB and was associated with a higher rate of Rx completion and better safety [19]. A systematic review updated in 2017 showed that the efficacy and the safety profile of 3HR were similar to those of 6H [20]. Nonetheless, the recommendations for the treatment of LTBI are generally based on studies carried out among patients in other risk situations for developing the disease as relatively few studies have evaluated the efficacy of the various preventive treatment regimens specifically among patients initiating biologics. In addition, there

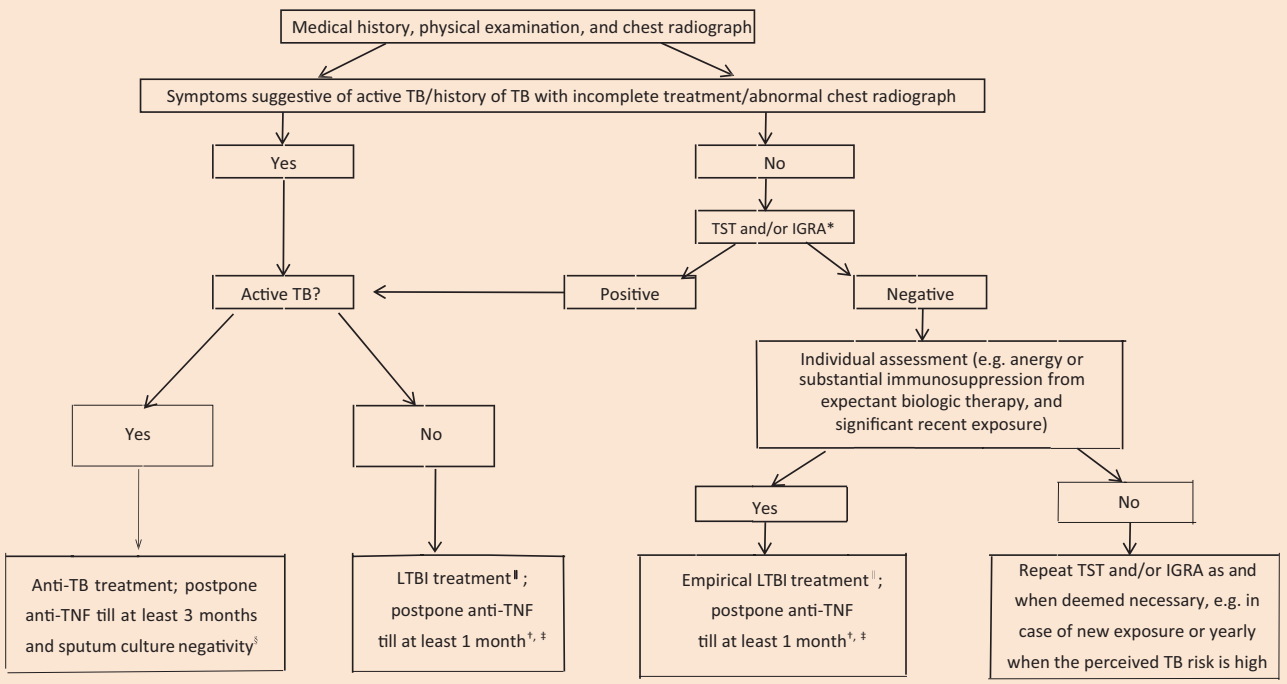
is limited data on the efficacy and safety of weekly rifapentine plus isoniazid for 12 weeks (3HP) in patients on biologics. Further studies on the relative performance of various treatment options in patients initiating biologics are needed. Basing on the available data, LTBI treatment with either 6–9H, 4R, or 3HR is recommended. Irrespective of the regimen used, the aim is to complete at least 1-month treatment before commencing biologic therapy [15,21,22]. Patients on LTBI treatment should be closely monitored for potential adverse effects from drugs especially hepatotoxicity and peripheral neuropathy. Any symptoms or signs suggestive of active TB should prompt further clinical assessment and investigation.

The stratification of TB risk will drive the biologic treatment choice. Non-anti-TNF targeted biologics are generally safer than anti-TNFs in LTBI positive patients with rheumatic diseases [23]. For patients with a perceived high TB risk and for whom LTBI treatment cannot be carried out, preference may be given to the use of a non-TNF inhibitor biologic to lower the risk of TB development.

Guideline statements (see algorithm in Figure 1)

Based on evidence on TB risk in patients initiating anti-TNF biologics, performance of currently available LTBI detection tools, effectiveness, safety,

Figure 1. Algorithm for evaluation of LTBI in patients before initiation of anti-TNF treatment.



TB = tuberculosis; LTBI = latent tuberculosis infection; anti-TNF = anti-tumor necrosis factor; TST = tuberculin skin test; IGRA = interferon-gamma release assay.

* Either TST or an IGRA is acceptable. Dual test may be considered in patients where the risk of progression to active TB disease is high, for example, those who are on systemic steroid therapy at the time of LTBI screening, or if infliximab therapy is anticipated.

† Educate patient on TB symptoms, monitor closely for TB with chest radiograph, sputum, and/or other tests as appropriate while on LTBI treatment and for at least 6 months thereafter.

‡ Consideration may be given to the use of a non-TNF inhibitor biologic to lower the risk of TB development in the scenarios where LTBI risk is high and LTBI treatment cannot be carried out.

§ Some international guidelines suggest to preferably initiate anti-TNF when a full course of anti-TB treatment has been completed [15].

‖ Suitable regimens may include isoniazid at a daily dose of 5 mg/kg (maximum 300 mg) for at least 6 to 9 months, rifampicin given at a daily dose of 10 mg/kg (maximum 600 mg) for 4 months or daily rifampicin plus isoniazid for 3 months. Pyridoxine at a daily dose of 10 mg is recommended in patients at risk for peripheral neuropathy when isoniazid is used.

and treatment completion rates from various LTBI treatment options as detailed above, the LTBI Working Group under the Tuberculosis Control Coordinating Committee of the DH and the HA has developed the following guideline statements on the management of LTBI in patients initiating anti-TNF biologics. The health care provider should choose the mode of screening and treatment of LTBI based on individual patient attributes and preferences, risk for progression to TB (especially the more severe forms) and other considerations including implementation issues peculiar to each clinical setting.

1) Screening of LTBI prior to the use of biologics is indicated.
2) Evaluation by medical history, physical examination, and chest radiograph is mandatory.
3) Patients who have completed appropriate TB therapy do not appear to be at a higher risk of TB relapse when anti-TNF therapy is initiated. In this situation, chest X-ray and sputum examination will be sufficient, with input from a TB specialist. Preventive chemotherapy is not generally recommended unless re-infection with MTB is plausible [13–15].
4) Should there be symptoms suggestive of active TB/history of TB with incomplete or inadequate treatment/abnormal chest radiographs, active TB should be ruled out by appropriate microbiological, radiologic, and pathologic studies, when necessary in consultation with a TB specialist for further assessment and management. Active TB has to be adequately treated before the commencement of biologic therapy.
5) LTBI screening is done by either Mantoux TST using two units of PPD-RT23, or IGRA using either QFT-Plus or T-SPOT.TB. TST is considered positive when induration ≥10 mm (≥5 mm under immunosuppressant therapy). LTBI is diagnosed when either TST or IGRA yields a positive result. Patients with a positive TST or IGRA should be offered LTBI treatment as appropriate after ruling out active TB. In the presence of substantial immunosuppression where the risk of progression to active TB disease is high, dual testing with TST and IGRA may help reduce the risk of false-negative results. In the case of psoriasis, consider screening with IGRA alone, or with IGRA and concurrent TST (if dual testing is considered and if the skin condition permits) [18]. If the IGRA test result is indeterminate, IGRA test may be repeated. In case of anergy but in the presence of recent TB exposure or radiological evidence of inactive TB, empirical LTBI treatment may be considered.
6) LTBI should be treated with Isoniazid (5 mg/kg/day) for at least 6 to 9 months unless contra-indicated. Alternative regimens may include rifampicin given at a daily dose of 10 mg/kg (maximum 600 mg) for 4 months or daily rifampicin plus isoniazid for 3 months. Pyridoxine at a daily dose of 10 mg is recommended in patients at risk for peripheral neuropathy when isoniazid is used.
7) If there are no urgent indications for biologics treatment, it may be preferable to initiate LTBI treatment for a minimum of one month for tolerability before concomitant administration of biologics [15,17,18]. In exceptional scenarios, for example, high TB risk or where LTBI treatment cannot be carried out, preference may be given to the use of a non-TNF inhibitor biologic to lower the risk of TB development.
8) Clinical examination and liver function testing should be conducted before initiation of LTBI treatment, and may be repeated at monthly intervals thereafter and whenever the patient develops symptoms of hepatitis. LTBI treatment should be discontinued in symptomatic patients with a serum transaminase level exceeding three times the upper limit of normal or in asymptomatic patients with a serum transaminase level exceeding five times the upper limits of normal. Patients on isoniazid therapy should also be monitored for evidence of peripheral neuropathy monthly and instructed to suspend treatment and seek medical attention promptly in the case of symptoms of peripheral neuropathy.
9) Any symptoms or signs suggestive of active TB should prompt further clinical assessment and investigation. Regular CXR should be performed for example, yearly, or at any time in case of respiratory symptoms during biologic treatment, and also afterwards especially for those who have been treated with infliximab. CXR may be performed more frequently during the first year if the perceived risk of TB is particularly high. Be aware that active TB on anti-TNF therapy may be disseminated and extrapulmonary; and that patients may present with unexplained weight loss, night sweats, lymphadenopathy, or symptoms referable to other organ systems.

10) Testing with TST and/or IGRA should be repeated in the presence of new exposure for patients whose initial screening test results are negative, taking into account the time window for test conversion. Repeat screening, for example, yearly, may also be considered if the perceived risk of TB is particularly high while on anti-TNF biologics.

CONCLUSIONS

The use of biologics especially anti-TNF agents has been well reported to be associated with an increased risk of TB activation in patients with chronic immune-mediated inflammatory disease such as rheumatic diseases, dermatologic diseases and inflammatory bowel diseases. Clinicians managing patients should screen for LTBI prior to initiation of anti-TNF biologics, in consultation with TB specialists if necessary. Notwithstanding preventive therapy, clinicians should maintain vigilance for TB in all patients who are put on biologics. It is mandatory that data on the safety of newer generations of biologics as well as the newer targeted synthetic drugs be captured, to inform further updates of guidelines and clinical decision-making.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

CKYO'Y, KMH, HS, and CKC contributed to all aspects of the development, evidence review, writing, editing, and final approval of this manuscript. CHC, TYWM, and CCL contributed by reviewing and discussing the evidence, finalizing the wording of the consensus statements, and provided review and edits to the manuscript.

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