



Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: management

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Because anti-tumor necrosis factor (anti-TNF) therapy has become increasingly popular in many Asian countries, the risk of developing active tuberculosis (TB) among anti-TNF users may raise serious health problems in this region. Thus, the Asian Organization for Crohn's and Colitis and the Asia Pacific Association of Gastroenterology have developed a set of consensus statements about risk assessment, detection and prevention of latent TB infection, and management of active TB infection in patients with inflammatory bowel disease (IBD) receiving anti-TNF treatment. Twenty-three consensus statements were initially drafted and then discussed by the committee members. The quality of evidence and the strength of recommendations were assessed by using the Grading of Recommendations Assessment, Development, and Evaluation methodology. Web-based consensus voting was performed by 211 IBD specialists from 9 Asian countries concerning each statement. A consensus statement was accepted if at least 75% of the participants agreed. Part 2 of the statements comprised 3 parts: management of

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latent TB in preparation for anti-TNF therapy, monitoring during anti-TNF therapy, and management of an active TB infection after anti-TNF therapy. These consensus statements will help clinicians optimize patient outcomes by reducing the morbidity and mortality related to TB infections in patients with IBD receiving anti-TNF treatment. (**Intest Res 2018;16:17-25**)

Key Words: Tuberculosis; Anti-tumor necrosis factor; Inflammatory bowel disease; Consensus statement

INTRODUCTION

Part 2 of the Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis (TB) infection in patients with IBD receiving anti-tumor necrosis factor (anti-TNF) treatment focused on management of latent TB in preparation for anti-TNF therapy, monitoring during anti-TNF therapy, and management of an active TB infection after anti-TNF therapy. As with Part 1, the quality of evidence and the strength of recommendations were assessed by using the Grading of Recommendations Assessment, Development, and Evaluation methodology. A consensus statement was accepted if at least 75% of the participants agreed.

MANAGEMENT OF LATENT TB IN PREPARATION FOR ANTI-TNF THERAPY

All patients with IBD diagnosed as having latent TB should be treated with a therapeutic regimen for latent TB prior to the initiation of anti-TNF therapy

- Quality of evidence, moderate; recommendations, strong
- Level of agreement: strongly agree 55%, agree 37%, uncertain 3%, disagree 3%, strongly disagree 2%

Anti-TNF therapies are associated with a 2- to 8-fold increased risk of active TB in patients receiving them compared with that in the general population.¹⁻⁴ Moreover, the risk of active TB was further increased when anti-TNF was used in combination with other immunosuppressants compared with that when anti-TNF monotherapy was used.⁵ Most of the active TB cases occurred within 3 to 4 months after anti-TNF therapy initiation; thus, reactivation of latent TB infection (LTBI) is considered to be the main cause rather than a new infection.¹ For these reasons, screening and treatment for LTBI before initiating anti-TNF therapy are strongly recommended by many scientific organizations and health authorities worldwide.⁶⁻¹⁹

The strict recommendation of chemoprophylaxis for LTBI has reduced the incidence of new TB cases among infliximab users from 11 patients in the first 2,000 infliximab users

to only 2 patients in the second 2,000 registrants.²⁰ Therefore, to reduce the risk of active TB, all patients with IBD diagnosed as having LTBI should be treated with a therapeutic regimen for latent TB prior to initiating anti-TNF therapy.

Chemotherapy for LTBI is not necessary for individuals with a history of proper treatment of TB unless there is a suspicion of a newly acquired infection

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 24%, agree 63%, uncertain 10%, disagree 3%

Because patients who had completed a full course of anti-TB treatment in the past do not seem to have an increased risk of developing TB while receiving anti-TNF therapy, tests for a TB infection are not considered to have significant clinical meaning, and LTBI treatment is not generally recommended unless there is a suspicion of a newly acquired TB infection.^{15,17} In a French study, even the reinitiation of anti-TNF after appropriate anti-TB treatment did not induce a reactivation of *Mycobacterium tuberculosis* (MTB) during the mean follow-up period of 42.7 months (range, 18–60 months) in patients with TB as a complication of anti-TNF therapy.²¹ Therefore, the decision to treat LTBI in these patients should depend on a new contact history with patients with active TB. When the appropriateness of prior anti-TB treatment is unclear, the decision to treat LTBI depends on the physician.¹⁵ In cases with a history of inappropriate anti-TB treatment, the possibility of active TB should be excluded prior to the initiation of LTBI treatment.¹⁵

The recommended treatment regimens for LTBI may vary among different countries

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 35%, agree 63%, uncertain 1%, disagree 1%

To date, the effectiveness of various treatment regimens for LTBI has not been evaluated in prospective controlled trials. The recommended treatment regimens for LTBI may vary according to specific geographic areas or the patient's

epidemiological background. Daily isoniazid (INH) for 12 months and daily INH plus rifampicin (RFP) for 3 months exhibited the best clinical efficacy, providing patients with >90% protection.¹⁷ However, daily INH for 9 months is considered the standard regimen for treating LTBI in many countries, including Australia,²² Canada,¹⁴ France,²³ Japan,¹⁰ Korea,¹⁹ Spain,²⁴ and Switzerland.²⁵ Moreover, randomized trials have shown that after the successful completion of daily INH for 9 and 6 months, the protection rates against TB reactivation were approximately 90% and 60%–80%, respectively.²⁶ The major disadvantage of 9-month daily INH is poor compliance owing to the long duration of treatment and hepatotoxicity.²⁷

Recently, shorter regimens such as daily RFP for 4 months or daily INH plus RFP for 3 months are being aggressively studied to improve the treatment completion rate.^{27,28} Currently, 4 months of daily RFP is recommended as a second-line therapy in the United States, Japan, and Saudi Arabia,^{8,26,29} whereas 3 months of daily INH plus RFP is recommended in the United Kingdom,¹⁶ based on long-term experience.^{27,28} Three months of daily INH plus RFP and 4 months of daily RFP are recommended as an alternative treatment to daily INH for 9 months in South Korea.¹⁹ Because both INH and RFP may be associated with hepatotoxicity, underlying liver diseases should be assessed before initiating LTBI treatment. Two months of daily RFP plus pyrazinamide was recommended as an LTBI treatment strategy in the year 2000 in the United States.²⁶ However, this combination was subsequently excluded as an approved LTBI treatment strategy after several reports of deaths resulting from severe liver toxicity.³⁰ Although 3 months of a daily combination of INH plus rifapentine (once a week for a total of 12 intermittent treatment sessions) has been approved and recommended for treating LTBI in the United States since 2011, rifapentine is not yet available in many countries.³¹

Even after LTBI is treated prior to commencing anti-TNF therapy, active TB may develop during the course of treatment. For this reason, the decision to treat LTBI should be readdressed after contact with patients with active TB again. The treatment regimen for LTBI in this case should be decided based on the drug sensitivity results of the index case (patient with active TB).¹⁹

In summary, treatment options recommended for LTBI include 6 months of daily INH, 9 months of daily INH, 3 months of weekly rifapentine plus INH, 3 to 4 months of daily INH plus RFP, or 3 to 4 months of daily RFP alone.³² The recommended treatment regimens for LTBI may vary among different countries.

When latent TB is found in patients with IBD who are planned for anti-TNF therapy, it should be postponed for at least 3 weeks after commencing LTBI treatment; however, the simultaneous initiation of LTBI and anti-TNF therapies may be considered in urgent cases

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 18%, agree 63%, uncertain 16%, disagree 2%, strongly disagree 1%

Many experts suggest that the time interval between the commencement of LTBI treatment and initiation of anti-TNF therapy is dependent on the patient's individual risk of TB reactivation and their urgent need for anti-TNF therapy to control disease activity. In general, most of the guidelines recommend starting anti-TNF 3 to 4 weeks after initiating LTBI prophylaxis; however, no large cohort studies have been conducted on the optimal time interval between the initiation of LTBI treatment and anti-TNF therapy. This recommendation is based on the observation that starting anti-TNF therapy 1 month after LTBI prophylaxis in LTBI-positive patients with rheumatoid arthritis significantly reduced the risk of TB reactivation.^{24,33,34} Furthermore, some experts recommend that if the activity of underlying disease and the global status of the patient permit, waiting for 1 additional month may be more beneficial because most of the adverse effects caused by INH treatment occur within the first 2 months of therapy.²⁴ However, in case of greater clinical urgency or with specialist recommendations to avoid surgical intervention, the simultaneous initiation of LTBI and anti-TNF therapy may be considered based on a shared decision making between the patient and physician, after an informed discussion of the benefits and risks; however, evidence for this practice is currently unavailable.

MONITORING DURING ANTI-TNF THERAPY

Even after LTBI is treated prior to initiating anti-TNF therapy, active TB may develop during anti-TNF therapy

- Quality of evidence, moderate; recommendations, weak
- Level of agreement: strongly agree 25%, agree 62%, uncertain 12%, disagree 1%

It has been observed that the treatment of LTBI prior to starting anti-TNF therapy reduces the risk of MTB reactivation. Randomized trials have shown that after the successful completion of a 9- and 6-month daily INH treatment, the protection rates against MTB reactivation were approximately 90% and 60%–80%, respectively.²⁶ However, concerns about the risk of active TB infection among anti-TNF users, even after LTBI treatment, remain. The clustering of

TB reports shortly after the initiation of anti-TNF therapy is consistent with the reactivation of LTBI owing to incomplete TB eradication with the currently recommended regimens, especially for INH-resistant MTB.³⁵ In some cases, however, it occurs later and may represent exogenous new infections after the eradication of LTBI.³⁶⁻³⁹

In a multicenter, retrospective study from Spain, 60% (30/50) of TB cases in anti-TNF-treated patients with IBD developed TB despite properly following the national guidelines for LTBI treatment, including 5 patients who received LTBI chemoprophylaxis.¹³ In a retrospective observational study from Greece, of 36 patients who completed LTBI treatment prior to anti-TNF therapy, 7 developed active TB at 2 to 35 months after anti-TNF therapy initiation.⁴⁰ In a retrospective observational study from South Korea, the active TB incidence was 1,107 per 100,000 patient-years in LTBI-positive anti-TNF users who received standard LTBI treatment and 490 per 100,000 patient-years in LTBI-negative anti-TNF users.⁴¹ Therefore, even after LTBI was treated prior to anti-TNF therapy, active TB cannot be completely prevented during anti-TNF therapy. For this reason, the possibility of TB development should always be considered.

Patients with IBD undergoing anti-TNF therapy should be regularly monitored for symptoms and signs suggesting the development of active TB

- Quality of evidence, moderate; recommendations, strong
- Level of agreement: strongly agree 67%, agree 30%, uncertain 3%

The development of active TB cannot be completely prevented during anti-TNF therapy despite LTBI treatment owing to the reactivation of LTBI caused by incomplete TB eradication with the currently recommended regimens and the risk of new infections resulting from close contact with infectious patients with TB in countries with a high prevalence of TB, even after the successful eradication of LTBI.^{13,36,39-41} Occasionally, active TB can be detected as an incidental finding on a chest radiograph during a regular check-up in asymptomatic patients. For this reason, the development of TB during anti-TNF therapy should carefully be monitored.

Although the negative conversion of interferon-gamma releasing assay (IGRA) is observed in some patients, most of the patients with positive tuberculin skin test (TST) or IGRA results at baseline will have positive test results even after the successful treatment of LTBI.^{42,43} Currently, there is no method of confirming whether LTBI has been adequately cured

after the completion of LTBI treatment. Therefore, monitoring should be based only on clinical symptoms and the signs of recurrent TB. The most frequent symptoms at the presentation of TB are fever, weight loss, respiratory symptoms, enlarged lymph nodes, and fatigue.¹³ Because more than half of these patients present with extrapulmonary or disseminated disease, abdominal pain, diarrhea, ascites, dysphonia, and headache may be the presenting symptoms.¹³ Therefore, a high level of clinical attention should be paid to patients with typical symptoms, such as an unexplained fever with or without weight loss, and those with atypical symptoms, to avoid a delay in diagnosis. Most anti-TNF-related TB cases occur within 3 to 6 months after initiating anti-TNF therapy. Thus, a short-term, regular follow-up to monitor symptoms and signs is critical during the first several months in these patients.^{1,44}

In patients without LTBI prior to anti-TNF therapy, an annual TST and/or IGRA are recommended in the Canadian,¹⁴ Italian,⁹ Swiss,²⁵ and United States.⁴⁵ guidelines, especially in patients with a high risk for MTB infection. Serial TST and IGRA testing may be useful to identify initial false-negative cases of LTBI and new TB infections during long-term anti-TNF therapy, especially in areas with a high TB burden. In addition, the risk of TST (+) conversion was found to significantly increase during 3 years of anti-TNF therapy.⁴⁶ To minimize this problem, some experts emphasize repeating the TST or IGRA tests annually for patients on long-term anti-TNF therapy.⁴⁷⁻⁴⁹ However, the necessity of regular TB infection tests is not universally recommended at present.

Exposure to active TB during anti-TNF therapy should prompt reevaluation for active TB or LTBI

- Quality of evidence, low; recommendations, strong
- Level of agreement: strongly agree 44%, agree 52%, uncertain 4%

Patients with IBD receiving anti-TNF therapy who have close contact with infectious patients with TB have a high risk of developing active TB or LTBI.^{15,19} Therefore, studies for diagnosing active TB and LTBI should be immediately performed in these patients.^{15,19}

Chest radiography should be performed to exclude active TB regardless of typical or atypical TB symptoms. Performing a retest has no clinical relevance for patients who were already positive for TST or IGRA prior to starting anti-TNF therapy, and the decision to start LTBI treatment should be based on only the clinical factors of these patients.^{15,19} If the MTB infection tests were negative prior to starting anti-

TNF therapy, a re-test should be performed immediately to confirm a positive conversion. However, in most cases, TB infection tests need to be repeated 8 to 10 weeks after close contact with infectious patients with TB because positive conversion takes 2 to 10 weeks (window period) after TB infection.^{15,19,50,51} Moreover, LTBI treatment should be initiated during this window period.

Compared with TB in the general population, patients who develop TB while on anti-TNF therapy have mostly severe and atypical disease, exhibiting a higher probability of extrapulmonary and disseminated manifestations

- Quality of evidence, low; recommendations, strong
- Level of agreement: strongly agree 27%, agree 55%, uncertain 16%, disagree 2%

MTB infection in patients undergoing anti-TNF therapy is more commonly extrapulmonary and disseminated compared with that in the general population.^{1,13,36,40,52-54} The physiopathology of disseminated TB may help understand this phenomenon. Alveolar macrophages, contaminated by MTB during the infectious process, induce the production of TNF- α . TNF- α is a key protective cytokine against MTB that, together with TNF-dependent chemokines, plays a critical role in the process of granuloma formation, preventing the dissemination of MTB.⁵⁵⁻⁵⁷ After the initiation of anti-TNF therapy, the process of granuloma formation is impaired, promoting the dissemination and reactivation of MTB.⁵⁴

In the general population, <20% of TB cases represent extrapulmonary forms and only 2% of patients exhibit disseminated disease.¹³ However, when TB occurs in patients on anti-TNF therapy, up to 60% represent extrapulmonary forms and approximately 25% of patients exhibit disseminated disease. Furthermore, the mortality rate has been reported to be as high as 17% in these patients.^{1,40}

MANAGEMENT OF ACTIVE TB INFECTION AFTER ANTI-TNF THERAPY

If active TB is diagnosed during anti-TNF therapy, anti-TNF therapy should be withheld, and anti-TB therapy should be commenced

- Quality of evidence, low; recommendations, strong
- Level of agreement: strongly agree 48%, agree 45%, uncertain 4%, disagree 3%

If active TB develops during anti-TNF therapy, anti-TNF therapy should be withheld and anti-TB therapy should be commenced;^{6,58} however, the British guidelines recommend

that anti-TNF therapy can be continued if clinically indicated because the patient would otherwise be prevented from receiving the continued clinical benefit to their underlying disease and may experience a flare-up or major clinical deterioration.¹⁶

Although there are little data on the impact of immunomodulators on the risk of TB in patients also receiving anti-TNF therapy, the results from a small case-control study in patients with rheumatoid arthritis revealed that the risk of active TB among corticosteroid, thiopurine, or methotrexate users was not increased.³⁷ This suggests that these medications do not need to be discontinued during anti-TB therapy, although larger studies are warranted.

The duration of treatment for active TB that occurs during anti-TNF therapy is not different from that of ordinary TB

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 31%, agree 44%, uncertain 17%, disagree 7%, strongly disagree 1%

The optimal duration of anti-TB therapy for active TB that occurs during anti-TNF therapy has not been well defined. Moreover, there is no evidence that the duration of anti-TB therapy needs to be prolonged if active TB occurs during anti-TNF therapy.¹⁷ Therefore, the duration of treatment for active TB that occurs during anti-TNF therapy is not different from that of ordinary TB.¹⁵

It is considered safe to delay the resumption of anti-TNF therapy until the completion of anti-TB therapy; however, anti-TNF therapy may be restarted after 2 months of anti-TB therapy if patients demonstrate a favorable response to anti-TB therapy and require the early resumption of anti-TNF therapy

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 12%, agree 65%, uncertain 19%, disagree 4%

Although there have been no prospective or controlled studies on the ideal timing of initiating anti-TNF therapy once anti-TB therapy has been initiated, it is considered safe to delay the resumption of anti-TNF therapy until the completion of anti-TB therapy. However, the reinitiation of anti-TNF therapy may be considered after 2 months of intensive anti-TB therapy if the patients satisfy all of the following conditions: TB was not initially severe; patients demonstrated a favorable response to anti-TB therapy; drug susceptibility is proven; and there is an urgent need for the early resumption of anti-TNF therapy.^{7,58} In 2 retrospective cohort studies, there were neither complications in the TB course nor cases

of TB relapse after the early retreatment with anti-TNF after initiating anti-TB therapy in patients with IBD with active TB during anti-TNF therapy.⁵⁹ Theoretically, if anti-TB therapy was appropriately performed, the associated immunosuppressed state should not interfere with the response to anti-TB therapy but rather accelerate the sputum culture conversion.^{59,60} However, there remain insufficient data in this regard.

Paradoxical reaction comprising a favorable response of MTB to anti-TB medication but worsening of the clinical, biological, or radiological findings of TB owing to an enhanced immune response can occur within a few months after the initiation of anti-TB treatment and anti-TNF withdrawal

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 16%, agree 69%, uncertain 15%

A paradoxical reaction, also called immune reconstitution inflammatory syndrome (IRIS), comprising a favorable response of MTB to anti-TB medication but worsening of clinical, biological, or radiological findings of TB, can occur within a few months after the initiation of anti-TB therapy and withdrawal of anti-TNF.^{61,62} The condition results from the rapid recovery of MTB-specific immune responses by the host after the withdrawal of anti-TNF therapy. In addition, there is a latent period between the initiation of anti-TB therapy and the development of the paradoxical reaction because the effect of anti-TNF will persist for 3 to 4 weeks after withdrawal.⁶³ The frequency of anti-TNF-associated TB-IRIS in the RATIO registry was 7%; the IRIS-associated factors comprised disseminated TB, a history of MTB exposure, and steroid use at the time of TB diagnosis.⁶⁴

Although the early diagnosis of IRIS remains difficult, identifying negative conversion is of great importance in patients with bacteriologically confirmed TB.¹⁵ Physicians should be aware of this condition because prolonged anti-TB therapy is not required; however, paradoxically, systemic corticosteroid use or the reintroduction of anti-TNF therapy may result in a more favorable outcome in severe cases.⁶⁵

CONCLUSIONS

Routine LTBI screening and prophylactic treatment is currently recommended as the standard of care for patients with IBD who are under consideration for anti-TNF therapy. These consensus statements will help clinicians optimize patient outcomes by reducing the morbidity and mortality related to TB infection in these patients. Further research is

required to develop more sensitive and specific tests to detect LTBI without being influenced by immunosuppressive medications and identify more effective and safe regimens for LTBI treatment.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

D.I.P., collecting and interpreting data, drafting the manuscript; S.K.Y., planning and conducting study, redrafting the manuscript; T.H., M.C., S.C.N., C.J.O., S.C.W., R.B., I.N.H., Y.T.J., D.S.H., H.J.K., Z.R., K.W., J.Q., P.J.H., K.M., A.A., Y.S., K.S., M.W., T.H., and A.S.P., collecting and interpreting data, redrafting the manuscript.

All of authors has approved the final draft submitted.

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