SPECIAL REVIEW: Consensus on TB in IBD

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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 1: risk assessment

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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 1 of the statements comprised 2 parts: risk of TB infection

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during anti-TNF therapy, and screening for TB infection prior to commencing 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;16:4-16)**

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

INTRODUCTION

Approximately one-third of the worldwide population is estimated to be infected with *Mycobacterium tuberculosis* (MTB).[1] Of these infected individuals, 10% develop an active tuberculosis (TB) infection and the remaining 90% develop a latent TB infection (LTBI), characterized by the presence of an immune response against MTB despite the absence of signs or symptoms of TB disease.[2] However, LTBI may progress to active TB if there is an imbalance in the host immune regulation caused by human immunodeficiency virus infection, malnutrition, malignancy, or treatment with immunosuppressive agents such as anti-tumor necrosis factor (anti-TNF) agents. TNF-α plays a central role in the host defense against MTB, particularly in the formation and maintenance of granulomas, limiting the dissemination of infection.[3,4] Therefore, the inhibition of TNF-α can increase the susceptibility to MTB and accelerate the reactivation of LTBI.[5]

Anti-TNF therapy initiated a new therapeutic era against chronic immune-mediated inflammatory diseases such as IBD and is recommended as the standard care for patients who fail to respond to conventional treatment in countries where the health-care system can afford its high cost.[6] However, shortly after the launch of anti-TNF treatment, the incidence of active TB increased among anti-TNF users throughout North America and Europe.[7] Previous studies based on the national registry of anti-TNF recipients also revealed an increased risk of TB in patients who were treated with anti-TNF agents.[8,9] Most cases developed within several months after the initiation of anti-TNF therapy, suggesting a reactivation of LTBI; however, delayed cases consistent with new infections have been occasionally reported.[7] The incidence of TB in patients with IBD receiving anti-TNF therapy may vary depending on the prevalence of TB in the general population, type of anti-TNF agent used, and type of underlying disease.[10] Because anti-TNF therapy has become increasingly popular in many Asian countries, where the prevalence of LTBI is much higher than that in Western countries, the risk of active TB among anti-TNF users may raise serious health problems in this region.[11,12] The incidence of TB among anti-TNF users has markedly decreased owing to routine LTBI screening and treatment in potential anti-TNF users.[13] Therefore, many scientific societies and national public health agencies currently recommend that all potential anti-TNF users should be screened for LTBI.[14-28] Moreover, this need for screening is required to a greater extent in many Asian countries, where the prevalence of LTBI is higher, than in Western countries. However, many questions remain unanswered concerning the need for screening, the best diagnostic approach, and preventive measures of LTBI prior to anti-TNF therapy, as well as concerning the appropriate management of active TB and the resumption of anti-TNF therapy after TB treatment. For this reason, the Asian Organization for Crohn's and Colitis and the Asia Pacific Association of Gastroenterology developed a set of consensus statements on the risk assessment, detection and prevention of LTBI, and management of active TB infection in patients with IBD receiving anti-TNF treatment. These recommendations will help clinicians optimize patient outcomes by reducing the morbidity and mortality associated with TB infection.

METHODS

The process and procedures for the development of consensus statements complied with the World Health Organization Guidelines Review Committee requirements, including the establishment of a guideline development panel, a systematic review of the evidence, and the formulation of recommendations by using a structured process.[29] After data appraisal, 23 consensus statements were initially drafted by D.I.P. and S.K.Y., and then discussed by the committee members; furthermore, the evidence was debated and the statements were redrafted several times. Although the draft was primarily based on published evidence, in some areas where the level of evidence was very low, reflecting the paucity of randomized controlled trials, expert opinions were included where required. Part 1 of the statements comprised 2 parts: (1) risk of TB infection during anti-TNF therapy, and (2) screening for TB infection prior to anti-TNF therapy.

The quality of evidence and the strength of recommendations were assessed by using the Grading of Recommenda-

tions Assessment, Development, and Evaluation (GRADE) methodology when applicable.[30] In the GRADE process, the quality of evidence of each statement was categorized as high, moderate, low, or very low. Evidence based on randomized controlled trials was initially classified as high-quality evidence but could be downgraded for several reasons, including study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias. Although data from observational studies (e.g., cohort and case-control studies) were initially classified as low-quality evidence, the rating could be upgraded if the magnitude of the treatment effect was substantial, if there was evidence of a dose-response relationship, or if all plausible biases were found to decrease the magnitude of an apparent treatment effect.[30,31] On the basis of the GRADE system, the strength of recommendations was classified as either strong or weak, as determined on the basis of 4 key factors: (1) quality of evidence; (2) balance of desirable benefits and undesirable harm; (3) values and preferences of clients and health-care providers; and (4) resource implications.[32]

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 voted 1 (strongly agree) or 2 (agree) on a scale of 1 to 5 (with 3, 4, and 5 indicating uncertain, disagree, and strongly disagree, respectively). If a statement was not accepted, the wording of the statement was discussed and revised, and then re-voting was conducted.[33]

RISK OF TB INFECTION DURING ANTI-TNF THERAPY

Reactivation of latent TB is increased in patients with IBD receiving anti-TNF treatment

- Quality of evidence, moderate; recommendations, strong
- Level of agreement: strongly agree 51%, agree 39%, uncertain 7%, disagree 3%

Although anti-TNF therapies have revolutionized the treatment of chronic immune-mediated inflammatory diseases, including IBD, these agents have been associated with a 2- to 8-fold increased risk of active TB in these patients compared with that in the general population.[34-37] Previous studies based on a national registry also revealed that anti-TNF therapy is associated with a nearly 4-fold increased risk of developing TB.[19,38] Because not all cases are reported, the actual risk is suspected to be higher than expected. In a systematic review of 40 randomized controlled trials with a total of 14,683 patients, the incidence of TB was 0.26% (26/10,010) in the anti-TNF group and 0% (0/4,673) in the control group receiving a placebo or placebo plus immunosuppressant, corresponding to an OR of 24.8 (95% CI, 2.4–133.0; P<0.01).[24] The risk of developing active TB was even greater when anti-TNF was combined with another immunosuppressant when compared with the control (OR, 54.0; 95% CI, 5.3–88.0) or anti-TNF monotherapy (OR, 13.3; 95% CI, 3.7–100.0) group.[24] According to a meta-analysis of randomized controlled trials for anti-TNF therapy in patients with IBD, the risk of TB infection among patients allocated to the anti-TNF therapy group increased 2.52-fold over that in those who received the placebo (95% CI, 0.62–10.21); however, the difference was not statistically significant.[39]

The risk of developing TB in patients receiving anti-TNF therapy may vary depending on the type of underlying disease and actual anti-TNF agent used.[8,40,41] Among 8,421 patients who were prescribed anti-TNF therapy in a Korean national database,[40] the incidence of TB (events per 10^5 person-years) was the highest in patients with IBD (3,710), followed by rheumatoid arthritis (1,143), psoriatic arthritis (934), and ankylosing spondylitis (715). The risk of developing TB may vary according to the specific anti-TNF agent, with higher risks reported with the use of the monoclonal antibodies infliximab and adalimumab relative to those reported with the use of the soluble TNF-receptor antagonist etanercept.[8,41]

Most of the active TB cases occurred within 3 to 4 months after the initiation of anti-TNF therapy. Thus, reactivation of LTBI rather than a new infection is considered to be the primary cause.[34] For these reasons, screening for LTBI before initiating anti-TNF therapy is strongly recommended by many scientific organizations and health authorities worldwide.[14-28]

The incidence rate of TB reactivation among patients with IBD undergoing anti-TNF therapy is higher in TB-endemic areas, including many Asian countries

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 34%, agree 48%, uncertain 17%, disagree 1%

Most new TB cases occur in Asia (59%) and Africa (26%), with a smaller proportion of cases occurring in Europe (5%) and North America (3%).[42] It has been estimated that almost one-third of the global population has LTBI. Moreover, LTBI is a growing concern, particularly in TB-endemic areas. For patients with IBD, the current incidence of active TB during anti-TNF therapy is approximately 1% to 2%.[43,44] The risk

of developing active TB in patients with LTBI is increased during anti-TNF therapy even after LTBI screening and treatment.[43] In TB-endemic areas, the risk of developing TB is also elevated by close contact with infectious patients with TB.

It has been suggested that the risk of developing TB among patients with IBD undergoing anti-TNF therapy might be substantially higher in TB-endemic areas, including many Asian countries, than in Western Europe or North America.[10] Comparing the nationwide registry databases of patients receiving anti-TNF for IBD and rheumatologic diseases, the reported number of TB cases per 10^5 person-years was 144 in the United States,[7] 130 in United Kingdom,[41] 117 in France,[8] 230 in Spain,[35] and 690 in Turkey.[45] In a nationwide database from South Korea, including 8,421 patients treated with an anti-TNF agent, the incidence of TB was 1,017 per 10^5 person-years.[40] In 4 retrospective cohort studies, including patients with IBD receiving anti-TNF treatment, conducted in South Korea,[46,47] Taiwan,[48] and Hong Kong,[49] the number of reported TB cases per 10^5 person-years was 1,997,[46] 2,484,[47] 1,900,[48] and 4,938,[49] respectively, per 10^5 person-years.

The risk of TB reactivation is higher when anti-TNF agents are combined with immunosuppressive agents

- Quality of evidence, moderate; recommendations, strong
- Level of agreement: strongly agree 35%, agree 43%, uncertain 20%, disagree 2%

In a systematic review of 40 randomized controlled trials, including 10,010 patients with anti-TNF therapy and 4,673 patients administered a placebo, TB reactivation was increased by 24.8-fold in patients who received anti-TNF therapy as compared with that in the control group (26/10,010 vs. 0/4,673; OR, 24.8; 95% CI, 2.4–133.0; P<0.001).[24] Moreover, TB reactivation increased 54-fold in patients treated with a combination of anti-TNF and immunosuppressive agents as compared with that in the control group (24/4,241 vs. 0/4,673; OR, 54.0; 95% CI, 5.3–88.0; P<0.001). TB reactivation also increased 13.3-fold in patients treated with a combination of anti-TNF and immunosuppressive agents compared with that in those with anti-TNF monotherapy (24/4,241 vs. 2/5,769; OR, 13.3; 95% CI, 3.7–100.0; P<0.001). It was suggested that the additional TB risk was related to a synergistic effect between the anti-TNF agents and methotrexate or azathioprine rather than the intrinsic risk of each immunosuppressive drug because the simple addition of immunosuppressive agents to the placebo group did not increase the risk of developing TB.

In another study using the Food and Drug Administration Adverse Event Reporting System between January 2003 and June 2011, the authors searched for "Primary Suspect" reports of various infections associated with anti-TNF, systemic corticosteroids, and immunosuppressive agents with a usage indication for IBD.[50] When analyzing TB infections, anti-TNF monotherapy was associated with an 8.5-fold increased risk of TB infection compared with 5-aminosalicylic acid therapy (OR, 8.52; 95% CI, 1.96–37.01; P<0.001). Combination therapies, including anti-TNF agents with an immunosuppressant (OR, 25.27; 95% CI, 5.66–112.72; P<0.001) or a systemic corticosteroid (OR, 3.17; 95% CI, 0.22–46.76; P=0.42) or both (OR, 24.28; 95% CI, 5.29–111.43; P<0.001), were similarly associated with an increased risk of TB infection compared with 5-aminosalicylic acid therapy. Therefore, more intensive LTBI screening and surveillance programs should be recommended for patients receiving combined anti-TNF agents and immunosuppressant and/or systemic corticosteroids.

Negative screening results do not exclude the risk of TB infection in patients with IBD receiving anti-TNF therapy

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 19%, agree 60%, uncertain 16%, disagree 5%

In 2 retrospective cohort studies from Spain[43] and Portugal,[51] as well as in a case report from India,[52] negative LTBI screening results from chest radiography and tuberculin skin test (TST) could not exclude the risk of TB infection in patients with IBD and rheumatologic diseases receiving anti-TNF therapy. Of 423 patients with IBD treated with anti-TNF, 7 (1.65%) developed TB during anti-TNF therapy.[43] Among the 7 patients who developed TB, 6 had negative LTBI screening results and 4 developed TB within the first 16 weeks after anti-TNF therapy initiation. Of 765 patients with rheumatologic diseases taking anti-TNF, 25 patients were diagnosed as having active TB.[51] Among the 17 patients tested for latent TB, 13 had negative TST results. These findings suggest that living in a region with high LTBI prevalence and concomitant immunosuppressant use, along with the low sensitivity of TST, may correspond to false-negative results in the LTBI screening protocol.

In an integrated analysis of LTBI screening data from 5 large phase III trials of golimumab in patients with rheumatologic diseases, 2,282 patients underwent both an interferon-gamma releasing assay (IGRA) and TST screening prior to golimumab treatment.[53] Among these patients, 13.8% had LTBI, including 9.4% with positive TST results, 7.0% with positive results in the QuantiFERON-TB Gold In-Tube

test (QFT-GIT; Cellestis, Carnegie, Australia), and 2.6% with positive results in both tests. Among the patients who had negative results in both TST and QFT-GIT during screening, 5 developed active TB during the 1-year follow-up. In a retrospective descriptive study conducted at 20 French and Swiss centers on all patients with IBD undergoing anti-TNF therapy who developed TB despite negative initial LTBI screening test results (thorough history and clinical examination, TST and/or QFT-GIT, chest radiography, or chest CT), 44 TB cases were identified.[54] Among the 6 patients who experienced a reactivation of LTBI (active TB diagnosed within the first 3 months), 4 patients underwent only TST and 2 were tested with only QFT-GIT. In a prospective study that included 426 patients with immune-mediated inflammatory diseases, both TST and QFT-GIT were performed before commencing anti-TNF therapy.[55] During a median of 297 days of follow-up, active TB developed in 1.4% (6/426) of the patients who tested negative for TST and QFT-GIT at baseline. In a retrospective cohort study of all TB cases identified out of 873 patients with IBD receiving anti-TNF therapy, 19 of 25 new TB cases developed despite negative LTBI screening with IGRA.[47] Therefore, we can reasonably conclude that negative screening results do not exclude the risk of TB infection in patients with IBD undergoing anti-TNF therapy. Based on the above facts, it is logical to suggest that all IBD patients who start anti-TNF therapy need to be closely monitored for reactivation of TB irrespective of the outcome of the screening tests.

SCREENING FOR TB INFECTION PRIOR TO ANTI-TNF THERAPY

Screening for latent or active TB should always be performed prior to commencing anti-TNF treatment

- Quality of evidence, moderate; recommendations, strong
- Level of agreement: strongly agree 91%, agree 9%

Systematic screening for LTBI or active TB should be considered at the time of initial diagnosis and always performed prior to commencing anti-TNF therapy. The introduction of LTBI screening protocols to candidate patients for anti-TNF therapy has had a beneficial impact on the incidence of active TB among Spanish patients with rheumatologic diseases. Patients exhibited a 21-fold higher risk of developing active TB compared with the general Spanish population before preventive actions were proposed. After the adoption of official recommendations, however, the development of active TB decreased by 78%.[13] 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.[56] The incidence of TB infection associated with anti-TNF therapy is higher in real-life clinical data than in controlled trials owing to the poor compliance with LTBI screening protocols. In a retrospective study performed at a large urban academic hospital in the United States, only 65% of patients were screened for LTBI prior to the initiation of anti-TNF therapy, and risk factors for TB were documented in only 17%.[57] Moreover, in a retrospective cohort study from South Korea, 18.5% of patients (161/873) did not undergo systematic screening for LTBI prior to initiation of anti-TNF therapy, and even in patients diagnosed with LTBI, a substantial proportion (13.7%, 10/73) did not receive prophylactic therapy.[47]

Screening for LTBI should be performed in patients before treatment with immunosuppressive drugs to avoid false-negative and inconclusive results. TST and the newer IGRA tests, including QFT-GIT and T-SPOT (T-SPOT.TB; Oxford Immunotec, Abingdon, UK), are often associated with false-negative and false-positive results, particularly in immunocompromised patients taking immunosuppressants or anti-TNF agents.[53] A previous study reported that the false-negative rate of TST reached as high as 40% in patients with rheumatoid arthritis.[58] In a large-scale meta-analysis of 124 studies, the pooled rate of the indeterminate results of QFT-GIT and T-SPOT increased from 2.1% (95% CI, 0.020–0.023) to 4.4% (95% CI, 0.039–0.050) and from 3.8% (95% CI, 0.035–0.042) to 6.1% (95% CI, 0.052–0.071), respectively, in immunocompromised patients.[59]

Latent TB is diagnosed on the basis of prior history of TB treatment and contact with patients with TB, chest radiography, TST, and/or IGRAs. There are local variations in the recommendations for utilizing these modalities

- Quality of evidence, high; recommendations, strong
- Level of agreement: strongly agree 55%, agree 42%, uncertain 2%, disagree 1%

Currently, there is no "gold standard" for the diagnosis of LTBI. International guidelines recommend a TB risk evaluation prior to commencing anti-TNF therapy. This evaluation is based on epidemiological risk factors (Table 1), physical examination, chest radiography, TST, and/or IGRA; however, there are local variations in the recommendations for utilizing these modalities.[14-28] A diagnosis of LTBI should be

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Table 1. Epidemiological Risk Factors for Latent TB Infection

Close contact with individuals known or suspected to have TB (family members or persons sharing living spaces)
History of active TB or radiologic findings suggestive of past TB that was not adequately treated
Living in or traveling to communities with high rates of latent or active TB
Low-income populations
Residents of long-term care and correctional facilities
Occupational exposure to high-risk groups (health-care workers)
Close contact with individuals known to have human immunodeficiency virus infection
Previous use of immunosuppressive drugs
Underlying diseases that predispose to MTB reactivation such as diabetes, cirrhosis, and alcoholism

TB, tuberculosis; MTB, *Mycobacterium tuberculosis*.

considered if any of the following criteria are satisfied; recent exposure to patients with active TB, positive initial or booster TST and/or positive IGRA; and no radiological evidence of active TB.[15]

Acquiring patient history includes obtaining treatment history and data about previous medications used for active TB or LTBI, history of BCG vaccination, and data on current symptoms of suspected TB (e.g., cough, hemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, and fatigue of >2 weeks duration) before being tested for LTBI. A physical examination should be conducted, specifically targeting the parts of the body affected by active TB. The purpose of performing a chest radiography is to confirm the absence of active TB and the presence of old healed lesions (calcification >5 mm, pleural thickening, linear opacities, or upper lobe fibronodular disease) with no history of anti-TB treatment.[60] Furthermore, Japanese guidelines recommend performing a chest CT in individuals with a high possibility of developing TB because minute lesions are occasionally detected on CT even when there are no abnormalities on a plain chest radiograph.[18]

In general, a TST should be considered positive if the induration is ≥5 mm; however, there are local variations (Table 2). A cutoff of 10 mm may be considered to reduce false positives in patients with no epidemiologic risk factors, but this decision should be individualized. Moreover, TST results can be distorted by a prior BCG vaccination because vaccinated individuals may become positive reactors to purified protein derivate. Therefore, different cutoffs are recommended for BCG-vaccinated (≥10 mm) and nonvaccinated (≥5 mm)

Table 2. Positive Cutoff Values of the Tuberculin Skin Test

Positive cutoff value	Country
≥5 mm	Brazil, Italia, Spain, Canada
≥10 mm in BCG-vaccinated and ≥5 mm in BCG nonvaccinated	China, Taiwan
≥10 mm in the general population and ≥5 mm in immunocompromised	Taiwan
≥10 mm	South Korea, France, Japan
≥15 mm in the general population and ≥10 or ≥5 mm in immunocompromised	Saudi Arabia
>15 mm in BCG-vaccinated and >6 mm in BCG nonvaccinated	United Kingdom

individuals in some countries (Table 2). This distortion is almost insignificant in adults aged >30 years, irrespective of the age at vaccination or revaccination.[15] TST may also be negative in patients who have been taking corticosteroids for >1 month or thiopurines or methotrexate for >3 months. Consequently, a booster TST may be appropriate for patients taking immunomodulators with a negative TST 1 to 2 weeks after the first test.[15]

Recently, IGRA (i.e., QFT-GIT and T-SPOT) has become commercially available in many countries. GFT-GIT and T-SPOT use purified antigens from MTB to stimulate peripheral blood lymphocytes for producing interferon-γ (IFN-γ). The QFT-GIT test measures the amount of IFN-γ in the supernatant of a cell suspension, whereas the T-SPOT test determines the number of cells producing IFN-γ with the use of an ELISpot assay. IGRA is increasingly being used for the diagnosis of LTBI owing to its higher specificity and sensitivity, particularly in immunocompromised hosts.[61,62] Moreover, IGRA does not exhibit any cross-reactivity with the BCG vaccine, which is another advantage of this method. Therefore, IGRAs may be particularly valuable for evaluating the TB infection status of individuals who had received a BCG vaccination.

Recent guidelines have changed the outlook concerning the diagnosis of LTBI. For example, the U.S. guidelines recommend replacing TST with IGRA as the diagnostic test for LTBI in all patients, and others recommend using both TST and IGRA either concomitantly or consecutively.[63-65] In addition, a recent publication from the United Kingdom verified that the LTBI detection rate was markedly increased when all 3 methods (clinical factors, TST, and IGRA) were used in combination.[66]

History of exposure to active TB should outweigh investigations for LTBI when considering chemoprophylaxis

- Quality of evidence, very low; recommendations, weak
- Level of agreement: strongly agree 21%, agree 62%, uncertain 8%, disagree 6%, strongly disagree 1%

Most of the international guidelines strongly recommend evaluating the risk of an MTB infection by taking an accurate clinical history including recent or past close contacts with patients with TB, being born in or having traveled to TB-endemic areas, being institutionalized, taking immunosuppressive drugs, and having underlying diseases associated with a predisposition to TB reactivation (e.g., diabetes, cirrhosis, and alcoholism) prior to initiating anti-TNF therapy.[14-20,22,23,25-28] In the RATIO registry, patients born in TB-endemic areas had a 10.3-fold higher risk of developing TB after anti-TNF therapy.[8] In a case report on a patient with UC who developed miliary TB after a second infusion of infliximab despite exhibiting a normal chest radiograph and negative IGRA test prior to starting infliximab, the patient had a history of very close contact with a patient with active pulmonary TB.[67] Another case of miliary TB was reported in a patient with IBD after 9 months of anti-TNF therapy despite several negative TSTs and indeterminate IGRA tests; however, the patient had a history of imprisonment for 4 years prior to the initiation of anti-TNF therapy.[68] In a prospective study comparing the predictive value of IGRA and TST for the progression of LTBI to active TB, 6 of 601 contacts progressed to TB disease within a 2-year follow-up period.[69] In a single-center cohort study from a TB-endemic country, taking a careful history of contact alone corresponded to 14 of 66 LTBI diagnoses (21%).[70]

TST and IGRA tests are associated with false-negative results, especially in immunocompromised patients taking immunosuppressants or anti-TNFs.[53,58] In a large-scale meta-analysis, the pooled rate of indeterminate results of IGRA was increased 2-fold in immunocompromised patients.[59] There is a significant false-negative rate associated with TST and IGRA; thus, a negative result does not rule out LTBI. Patients with a clear history of a recent or past exposure to active TB were also candidates for LTBI treatment. Therefore, if a clear history of recent or past close exposure to TB is obtained, chemoprophylaxis should be performed before initiating anti-TNF therapy.

Abnormal chest radiographs suggestive of old TB in patients without a history of treatment should be considered as LTBI after excluding active TB

- Quality of evidence, very low; recommendations, weak
- Level of agreement: strongly agree 20%, agree 57%, uncertain 16%, disagree 7%

All guidelines recommend taking a chest radiograph, particularly in groups at a high-risk for TB development, except for the American College of Rheumatology, which recommends taking a chest radiograph only in case of positive TB infection tests (TST and IGRA) and the presence of risk factors.[71] The purpose of obtaining a chest radiograph is to confirm the absence of active TB and the presence of old healed lesions (calcification >5 mm, pleural thickening, linear opacities, or upper lobe fibronodular disease) with no previous anti-TB treatment.[60] The relative risk of developing active TB in individuals with untreated old TB lesions is considered 6 to 19 times higher than that in persons with no known risk factors, which is the highest risk after advanced human immunodeficiency virus infection and close contact with infectious TB.[72] In a single-center cohort study from a TB-endemic country, chest radiography was an important test for providing additional evidence of LTBI because 9% of the positive screening results were exclusively due to an abnormal chest radiograph.[70] For individuals with untreated old TB lesions (except those with only pleural adhesion images or small calcification), prophylactic treatment with isoniazid (INH) for 24 weeks was reported to reduce the incidence of TB development by 65%;[73] therefore, LTBI treatment has been determined to be useful for untreated old pulmonary TB. However, the presence of small (≤5 mm) calcified pulmonary nodules alone does not merit LTBI treatment because these lesions rarely display viable organisms upon an autopsy study.[74] LTBI treatment is not indicated for patients with remaining fibrotic lesions if they had a history of adequate treatment for previous TB.

IGRAs are preferred over TST in BCG-vaccinated individuals, because TST exhibits cross-reactivity with the BCG vaccine, yielding false-positive results, whereas IGRAs do not

- Quality of evidence, high; recommendations, strong
- Level of agreement: strongly agree 45%, agree 45%, uncertain 10%

It is important to recognize that the sensitivity of TST is sufficient; however, its specificity for predicting LTBI is not because only about 5% of immunocompetent patients with

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a positive TST result may progress from LTBI to active TB disease in their lifetime.[75] A diagnosis of LTBI with TST may particularly be distorted by prior BCG vaccination because the purified protein derivatives used in the TST include antigens present in BCG strains, thereby leading to high false-positive results.[15] However, this distortion is almost insignificant in adults aged >30 years, irrespective of the age at vaccination or revaccination[15] because the frequency of a positive TST result is considerably reduced 2 years after vaccination, whereas no influence was observed after 10 years.[76,77]

The high false positivity of TST induced by prior BCG vaccination may be overcome through the use of 2 new IGRAs (GFT-GIT and T-SPOT), which detect T-cell-mediated IFN-γ responses to 2 specific MTB antigens (ESAT-6 and CFP-10),[14] which are absent in the BCG strain. Therefore, IGRAs may be particularly valuable for evaluating the LTBI status of individuals who had been vaccinated with BCG.[14]

Multiple studies, particularly in immunocompetent patients, have demonstrated that IGRA tests are more sensitive and specific than TST,[59,78,79] and their predictive value for the progression of LTBI to active TB disease has been demonstrated to be higher than that of TST, as observed in subjects with recent close contacts with patients with active TB.[69]

Both IGRAs and TST can provide false-negative results in patients receiving immunosuppressive treatment; however, IGRAs are less influenced by immunosuppressive medications than is TST

- Quality of evidence, low; recommendations, weak
- Level of agreement: strongly agree 26%, agree 67%, uncertain 6%, disagree 1%

Immunosuppressive therapy (chronic systemic steroids, azathioprine, 6-mercaptopurine, methotrexate) in patients with IBD may reduce the sensitivity, thereby increasing the false-negative results of TST by inducing anergy and further resulting in a lack of a delayed-type hypersensitivity reaction.[80-82] This limitation diminishes the ability of clinicians to rely on TST as an adequate screening method for LTBI and reinforces the importance of the proper interpretation of TST results based on a patient's risk factors.

IGRA is a more specific and sensitive test for the diagnosis of LTBI than TST in immunocompetent patients.[83] However, IGRA is also negatively influenced by immunosuppressive therapy.[84] Ferrara et al.[85] reported that patients receiving at least 1 immunosuppressive drug were three times more likely to have an indeterminate IGRA result than those not receiving such treatment (OR, 3.35; 95% CI, 1.84–6.08; P<0.0001). In a prospective case-control study,[86] patients with IBD receiving immunosuppressive therapy were associated with a significantly lower IGRA positivity rate than those not receiving the therapy (13.0% vs. 29.6%, P=0.002). This difference seemed most prominent in patients taking azathioprine (11.8% vs. 27.3%, P=0.006).

Both IGRA results (pooled OR, 0.37; 95% CI, 0.16–0.87; P=0.02) and positive TST results (pooled OR, 0.28; 95% CI, 0.10–0.80; P=0.02) are significantly influenced by immunosuppressive therapy;[79] however, IGRAs are less influenced by immunosuppressive medications than is TST.[26,68] Because the risk of developing TB is increased in patients with IBD taking immunosuppressive therapy, increasing the sensitivity may be more important than a slight decrease in the specificity for detecting LTBI. Therefore, the use of TST alone is not appropriate for detecting LTBI in patients with IBD receiving immunosuppressive therapy prior to the initiation of anti-TNF therapy.

The "either test positive" strategy is a valid method for diagnosing LTBI; however, its superiority to other strategies is unclear

- Quality of evidence, moderate; recommendations, strong
- Level of agreement: strongly agree 17%, agree 63%, uncertain 16%, disagree 4%

Since TB infection in patients with IBD receiving anti-TNF therapy may be severe, disseminated, and occasionally fatal, most experts agree that increasing sensitivity is more important than a slight decrease in specificity for detecting LTBI.[34,54,87] The concomitant use of 2 or more immunosuppressive drugs may lead to false-negative results in both TST and IGRAs, and some authors recommend using both methods to increase the sensitivity of detecting LTBI in immunosuppressed patients prior to initiating anti-TNF therapy.[88,89]

The recommended tests for diagnosing LTBI in immunosuppressed patients prior to initiating anti-TNF therapy may vary depending on the country. Some countries recommend TST first, followed by IGRAs in cases of a borderline or suspected false-negative TST or if a history of previous BCG vaccination is present. Others recommend the simultaneous use of TST and IGRAs for all cases. The Swiss Lung Association recommends that IGRAs are the only diagnostic test for LTBI;[90] however, TST alone is not recommended for detecting LTBI in most countries. Recently, the "either test positive" strategy (either test can be performed first, and if the test result is negative, then the other test can be performed) has

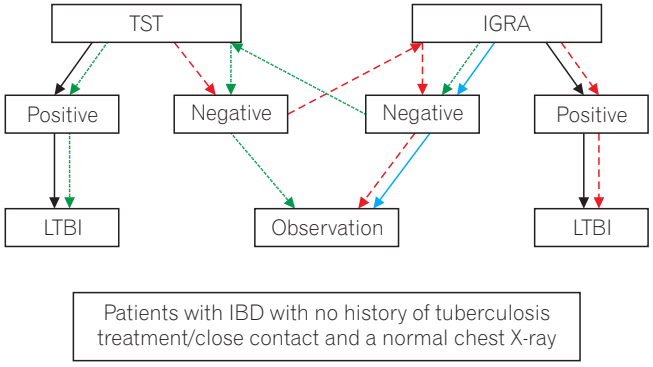

Fig. 1. Algorithm for the diagnosis of latent tuberculosis infection in patients with IBD. Blue arrow, if a history of BCG vaccination is present; red arrow, start with tuberculin skin test (TST); green arrow, start with interferon-gamma releasing assay (IGRA). LTBI, latent tuberculosis infection.

been reported to reduce the rate of TB development close to the incidence of the general population.[64] Therefore, we propose that the "either test positive" strategy is a valid method for diagnosing LTBI, although it is unclear whether it is superior to other strategies (Fig. 1).

SUMMARY

In summary, Part 1 of the Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on TB infection in patients with IBD receiving anti-TNF treatment highlighted the methodology in the development of the consensus statements, substantially higher risk of TB reactivation during anti-TNF therapy in many Asian countries, and various diagnostic tests for LTBI. Part 2 of the consensus statements highlight 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.

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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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SPECIAL REVIEW: Consensus on TB in IBD

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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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These consensus were developed and approved by the AOCC and APAGE, and are being published simultaneously in the *Intestinal Research* and *Journal of Gastroenterology and Hepatology.*

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

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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-

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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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