

TREATMENT GUIDELINES FOR LATENT TUBERCULOSIS INFECTION

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The Prevention Committee and the Treatment Committee
of the Japanese Society for Tuberculosis

Abstract The treatment of latent tuberculosis infection (LTBI) has been established as valid for patients at high risk for developing active tuberculosis. Treatment of LTBI is also considered an important strategy for eliminating tuberculosis (TB) in Japan. In recent years, interferon- γ release assays have come into widespread use; isoniazid (INH) preventive therapy for HIV patients has come to be recommended worldwide; and there have been increases in both types of biologics used in the treatment of immune diseases as well as the diseases susceptible to treatment. In light of the above facts, the Prevention Committee and the Treatment Committee of the Japanese Society for Tuberculosis have jointly drafted these guidelines.

In determining subjects for LTBI treatment, the following must be considered: 1) risk of TB infection/development; 2) infection diagnosis; 3) chest image diagnosis; 4) the impact of TB development; 5) the possible manifestation of side effects; and 6) the prospects of treatment completion. LTBI treatment is actively considered when relative risk is deemed 4 or higher, including risk factors such as the following: HIV/AIDS, organ transplants (immunosuppressant use), silicosis, dialysis due to chronic renal failure, recent TB infection (within 2 years), fibronodular shadows in chest radiographs (untreated old TB), the use of biologics, and large doses of corticosteroids. Although the risk is lower, the following risk factors require consideration of LTBI treatment when 2 or more of them are present: use of oral or inhaled corticosteroids, use of other immunosuppressants, diabetes, being underweight, smoking, gastrectomy, and so on.

In principle, INH is administered for a period of 6 or 9 months. When INH cannot be used, rifampicin is administered for a period of 4 or 6 months. It is believed that there are no reasons to support long-term LTBI treatment for immunosuppressed patients in Japan, where the risk of infection is not considered markedly high. For pregnant women, HIV-positive individuals, heavy drinkers, and individuals with a history of liver injury, regular liver function tests are necessary when treatment is initiated and when symptoms are present. There have been reports of TB developing during LTBI treatment; therefore, attention should be paid to TB development symptoms.

When administering LTBI treatment, patients must be educated about side effects, the risk of developing TB onset, and the risks associated with discontinuing medication. Treatment outcomes and support for continuation of treatment are evaluated in cooperation with health centers. As stipulated by the Infectious Diseases Control Law, doctors are required to notify a health center when an individual develops TB. Based on this notification, the health center registers the patient, sends a public health nurse to visit the patient and give instructions, and provides medication adherence support. The patient applies at a health center for public expenses for medical care at a designated TB care facility. Pending approval in a review by an infectious disease examination council, the patient's copayment is reduced.

1. Basic underlying view

Since the beginning of the 1950's, para-aminosalicylic acid (PAS) has been administered as an anti-tuberculosis (TB) drug to patients infected with TB in Japan in an attempt to prevent the development of TB¹⁾. In the United States, a large-scale controlled trial using isoniazid (INH) was conducted from the 1950's to the 1960's; subjects included children, families of incipient TB patients, patients at psychiatric facilities, Alaskan inhabitants, patients with inactive TB lesions, and military

veterans. A controlled trial was also conducted in Europe by the International Union Against Tuberculosis (IUAT). Based on these trials, chemical prophylaxis was established as valid for individuals infected with TB^{1,2)}. However, while the merits of development risk reduction due to chemical prophylaxis outweigh the demerits of the resultant side effects for patients at high risk for developing TB, it is unclear whether this applies to patients whose development risk is not high. Therefore, when a patient is infected with TB, common practice is to perform a TB infection test for patients at high risk for

developing TB.

Latent TB infection (LTBI) is a concept that has come into use since its description in a joint statement entitled “Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection” issued by the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) in 2000; the concept views *Mycobacterium tuberculosis* infection itself as a latent disease³⁾. Therefore, whereas chemical prophylaxis aims to prevent TB from developing into active disease, LTBI treatment is the treatment of latent disease. The ATS/CDC statement views LTBI treatment as a fundamental element in a TB elimination strategy. An elective tuberculin skin test (TST) is performed for high-risk people; treatment is considered important for those who test positive.

In February 2005, the Prevention Committee of the Japanese Society for Tuberculosis incorporated the view of the above-mentioned ATS/CDC joint statement in issuing its own joint statement with the Japan College of Rheumatology, entitled “Further Proactive Implementation of Chemical Prophylaxis”⁴⁾. A markedly inordinate number of TB patients in Japan are middle-aged or elderly; more proactive chemical prophylaxis is considered necessary for these patients. The effects of chemical prophylaxis have been widely recognized for the many middle-aged and elderly patients who have been infected in the past. Therefore, chemical prophylaxis is recommended for high-risk patients, such as patients with immunosuppressive factors and patients using corticosteroids or tumor necrosis factor- α (TNF- α) inhibitors.

The concept of LTBI is now widely used in Japan due to its inclusion in the revised notification criteria in June 2007⁵⁾. Previously, only people aged 29 years or younger were eligible for public medical expenses for preventive medication against primary TB. However, for LTBI treatment, public expenses are used regardless of age not only for new infections, but also for any patient considered at high risk for developing TB due to previous infection and immunosuppression; public expenses are paid on the condition that the patient undergoes a TST or an interferon- γ release assay (IGRA)⁶⁾.

The May 2011 revision of “Prevention Guidelines for Specific Infectious Diseases Related to Tuberculosis” (hereafter “Prevention Guidelines”) states under the item “Provision of Medical Care” that, “Treatment of latent tuberculosis infection is actively recommended”; the Prevention Guidelines also clearly state a target of “completion of treatment in at least 85% of cases of latent tuberculosis infection treatment”⁷⁾. In the future, LTBI treatment may also be an important strategy in Japan for eliminating TB.

Previous TSTs used to diagnose TB infections had problems with specificity due to the effects of past Bacillus Calmette-Guérin (BCG) vaccinations and nontuberculous mycobacteria. In contrast, IGRAs, which measure interferon- γ released from lymphocytes due to stimulation of TB-specific antigens, possess excellent specificity. QuantiFERON®-TB-2nd Generation use was initiated in April 2005, and QuantiFERON®-TB-

3rd Generation (QuantiFERON®-TB Gold In-Tube; hereafter “QFT-G”) is now in use as of 2010. Furthermore, T-SPOT®.TB (hereafter “T-SPOT”) has been covered by health insurance since November 2012. Please refer to the “Guidelines for Using QuantiFERON®-TB Gold In-Tube” published by the Prevention Committee⁸⁾ regarding the use of QFT-G.

In recent years, HIV testing among TB patients has expanded rapidly worldwide. In the 169 countries for which the state of HIV testing was reported in 2010, HIV infection was examined in 34% of TB patients⁹⁾. Although HIV patients have previously been included as subjects for LTBI treatment, there is a call for a more proactive approach, including in developing countries¹⁰⁾.

Additionally, based on the expansion of the types of biologics used in immune diseases (such as rheumatoid arthritis) as well as the list of diseases susceptible to biologics (Table 1), the number of patients who undergo LTBI treatment may increase. However, despite doctors who make a diagnosis of TB (including LTBI) being obligated to file a notification based on Article 12 of the Infectious Diseases Control Law, the number of patients who actually undergo LTBI treatment is believed to be considerably lower than the estimated number. This is inferred to result from the lack of awareness among doctors regarding the notification requirement, which in turn stems from the fact that many of the doctors and medical facilities that handle immune diseases are not specialized in TB.

Based on the above changes in the status of LTBI treatment and following the “Further Proactive Implementation of Chemical Prophylaxis”⁴⁾ statement published in 2005 by the Prevention Committee and the Treatment Committee of the Japanese Society for Tuberculosis, we have formulated the present guidelines based on the following principles:

- 1) To promote LTBI treatment as an important strategy for eliminating TB.
- 2) To incorporate new findings regarding IGRAs as a method for diagnosing infection, as well as new findings regarding treatment protocols.
- 3) To further promote LTBI diagnosis and treatment for the HIV infected.
- 4) To describe basic items regarding TB measures and related systems while considering that the list of diseases susceptible to biologics has expanded; biologics are used in various immune-mediated inflammatory diseases; and LTBI treatment is administered by doctors and medical facilities that are not specialized in TB.
- 5) To leave the details of LTBI treatment discovered through contact investigations and the Koch phenomenon to other publications.

Monitoring of the attributes, treatment implementation status, and subsequent TB development status of patients undergoing LTBI treatment is desirable for verifying the validity of the present guidelines.

Table 1 Biologics and susceptible diseases

Common name (trade name)	Susceptible diseases	Classification by efficacy
Infliximab (Remicade)	(1) Rheumatoid arthritis, (2) Ulcerative colitis, (3) Intractable retinal uveitis due to Behçet's disease, (4) Plaque psoriasis, (5) Psoriasis arthropathica, (6) Pustular psoriasis, (7) Erythrodermic psoriasis, (8) Ankylosing spondylitis, (9) Crohn's disease	Anti-human TNF- α monoclonal antibody
Etanercept (Enbrel)	Rheumatoid arthritis	Complete human soluble TNF- α /LT- α (*) receptor
Tocilizumab (Actemra)	(1) Rheumatoid arthritis, (2) Juvenile idiopathic arthritis with activity in multiple joints, (3) Systemic juvenile idiopathic arthritis, (4) Castleman's disease	Humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody
Adalimumab (Humira)	(1) Rheumatoid arthritis, (2) Plaque psoriasis, (3) Psoriasis arthropathica, (4) Ankylosing spondylitis, (5) Crohn's disease	Humanized anti-human TNF- α monoclonal antibody
Abatacept (Orencia)	Rheumatoid arthritis (only when effects in existing treatment are insufficient)	Selective T-cell costimulation modulator
Golimumab (Simponi)	Rheumatoid arthritis when effects are insufficient in existing treatment (including prevention of structural joint damage)	Humanized anti-human TNF- α monoclonal antibody
Ustekinumab (Stelara)	Plaque psoriasis when effects are insufficient in existing treatment, Psoriasis arthropathica	Humanized anti-human IL-12/23p40 monoclonal antibody
Certolizumab (Cimzia)	Rheumatoid arthritis when effects are insufficient in existing treatment (including prevention of structural joint damage)	TNF- α inhibitor (PEG-modified humanized anti-human TNF- α monoclonal antibody Fab fragment)
Canakinumab (Ilaris)	Cryopyrin-associated periodic syndromes (familial cold auto-inflammatory syndrome, Muckle-Wells syndrome, Neonatal-onset multisystem inflammatory disease)	Humanized anti-human IL-1 β monoclonal antibody
Rituximab (Rituxan)	1. CD20-positive B cell non-Hodgkin's lymphoma 2. Pre-administration injection of Indium-111 ibritumomab tiuxetan (genetic recombination) and Yttrium-90 ibritumomab tiuxetan (genetic recombination)	Anti-neoplastic agent, Anti-CD20 monoclonal antibody

*LT- α : Lymphotoxin- α (aka TNF- β)

2. LTBI treatment subjects

1. Basic view

In order to perform LTBI treatment effectively and efficiently in a state of low incidence, the selection of appropriate subjects is important; these subjects are people infected with TB who are at relatively high risk for developing active TB, and for whom the benefit of treatment outweighs the side effects³⁾. When applying an infection diagnosis or LTBI treatment, a comprehensive examination of the following items is necessary:

(1) Infection/development risk

The following are at high risk of TB infection: elderly people; socioeconomically vulnerable people, such as the homeless; people who have lived in a country with a high prevalence of TB; healthcare workers; and people held in correctional facilities.

Among people infected with TB, factors that lead to a high risk for developing active TB include the following: recent

infection (within the last 1–2 years); HIV infection; pneumoconiosis; chest radiograph findings consistent with past TB; being underweight; diabetes; hemodialysis due to chronic renal failure; gastrectomy; duodenileostomy; cardiac failure; head and neck cancer; use of drugs with an immunosuppressive effect, such as corticosteroids; and use of biologics such as TNF- α inhibitors³⁾⁴⁾¹¹⁾¹²⁾.

(2) Infection diagnosis and testing methods

TB infection is now diagnosed with IGRAs and TSTs. However, because TSTs are affected by BCG vaccinations, infection diagnoses in Japan have not been very accurate. Once IGRA came into use following the ATS/CDC joint statement, a cost-effectiveness analysis was conducted. This analysis found that it is more cost-effective to perform an infection diagnosis than to not perform one for the following groups of people: close contacts, HIV carriers, and foreign-born individuals (regardless of how long they have resided in the United States). In all of these groups, IGRA was more cost-effective than TSTs¹³⁾. Regarding cost-effectiveness analyses

related to LTBI screening, direct comparisons between studies that performed LTBI screening are impossible due to the effects of several factors: how the analysis model was devised; the duration of the follow-up period after testing; the cost of LTBI treatment; the cost of active TB treatment (in cases where active TB develops); the costs, sensitivities, and specificities of TSTs and IGRA; control group infection rates and BCG vaccination histories in TSTs and IGRA; and the risk of active TB developing from LTBI. However, in almost all of these studies, IGRA was a highly cost-effective screening method, whether performed alone or following a positive TST¹⁴⁾. As IGRA uses a TB-specific antigen, it is not affected by BCG vaccinations; therefore, IGRA is considered particularly useful in Japan and other countries with high coverage of BCG vaccination.

On the other hand, comparisons between QFT-G and T-SPOT used on patients with active TB have indicated that T-SPOT has higher sensitivity, whereas QFT-G has higher specificity¹⁵⁾¹⁶⁾; however, a recent report found no significant difference in specificity¹⁷⁾. Although many reports have stated that T-SPOT has high sensitivity, particularly in immunodeficiency, there is no gold standard for assessing LTBI; therefore, it is difficult to conclude that one testing method is better than the other¹⁸⁾.

(3) Chest image diagnosis

When beginning LTBI treatment, chest radiography must be performed. The purpose of chest radiography is twofold: to confirm the absence of active TB; and to confirm remaining old lesions due to natural healing following past TB development. When performing chest radiography, the diagnosis should be made by a doctor with experience in reading chest radiographs, such as a pulmonologist or a radiologist. Fine lesions are sometimes detected by computed tomography (CT) even when there are no abnormalities in a plain chest posteroanterior radiograph^{19)–21)}. Taking into account the cost and the amount of radiation exposure from CT, CT is considered valid for people with a high possibility of developing TB when beginning LTBI treatment. This includes people such as the following: those whose population has a high infection rate or someone who has already developed TB, those with immunological problems, and those with respiratory symptoms such as coughing or sputum.

(4) Impact of TB development

From the perspective of preventing secondary infections due to TB development, more proactive treatment is considered for certain types of people, such as those in professions that put them in constant contact with frail immune systems, and those who would affect a large number of people by developing TB due to living with a group. In addition, LTBI treatment is proactively considered in cases where the prognosis is anticipated to deteriorate. Such cases include those in which treatment in the event of TB development is anticipated to be

difficult due to complications, as well as cases in which TB development affects the treatment of complications.

(5) Possible manifestation of side effects

The advantages and disadvantages of treatment must be examined by considering the balance between 2 sides: the possible manifestation and seriousness of side effects due to the use of drugs, and the risk of developing TB. Caution is necessary when administering INH to patients with the following: liver injury, renal dysfunction, psychiatric disorders, alcoholism, convulsive disorders (or a past history of convulsive disorders), drug hypersensitivity, hematologic disorders, and bleeding tendency. Liver injury due to INH is believed to manifest frequently in people aged 30–35 years or older; in rare cases, such injury may become severe²²⁾. Therefore, INH should not be administered liberally when the risk of TB infection and development is unclear. The serious side effects of rifampicin (RFP) include the following: hepatic dysfunction, allergic reaction, influenza-like symptoms (as a type of allergy), and in rare cases, interstitial nephritis and myelosuppression.

Regarding LTBI treatment for pregnant women, although the attachment on INH states that it “should not be administered,” the ATS/CDC guidelines state that “Because conditions that promote hematogenous spread of organisms to the placenta (e.g., recent infection and HIV infection) or progression of LTBI to disease can endanger both the mother and baby, many experts agree that pregnant women with these conditions and LTBI should be treated during pregnancy and have careful clinical and laboratory monitoring for hepatitis”³⁾. In addition, regarding breastfeeding, while the attachment states that “Breastfeeding should be avoided,” the ATS/CDC guidelines state that “Breastfeeding is not contraindicated when the mother is being treated for LTBI. However, infants whose breastfeeding mothers are taking isoniazid should receive supplemental pyridoxine”³⁾.

(6) Treatment completion prospects

Due to the absence of subjective symptoms and physical findings, it is generally difficult for patients to consider LTBI as a disease; thus, patients tend to drop out of treatment or discontinue it. A cautious approach is necessary for those with a distinctly high likelihood of discontinuing treatment (for example, those going to a foreign destination where there is no LTBI treatment program), as such people may acquire resistance in cases where treatment is forced, resulting in the development of TB. As described in a recent report, directly observed therapy consisting of INH and rifapentine administered once a week for 3 months (12 times in total) is considered a useful treatment for patients at high risk for discontinuing treatment²³⁾. Future examination (including approval of rifapentine) is necessary in Japan as well.

2. TB development risk factors and infection diagnosis

The application of LTBI treatment is based on the risk factors of TB development and the interpretation of infection diagnosis results in that situation. As described below, caution is necessary regarding the significance of these risk factors and infection diagnoses in those respective risk factors.

(1) Contact with an infectious patient

Among young people (who have a particularly low rate of past infections) who are identified to be infected in contact investigations, there is an extremely high possibility that the discovered infection is new. In recent years, new infections have become more likely among elderly people as well due to their declining rate of past infections. The probability of developing TB is believed to be 15 times greater for people who were infected within the past 2 years¹¹⁾; therefore, while taking into consideration infection risk in the patient's population and rates of positive IGRA results, such people are viewed as subjects for treatment provided they do not present with side effects or other problems. For a detailed view of contact investigations, please refer to the "Tuberculosis Contact Investigation Guide"²⁴⁾.

(2) Pathologies involving immunodeficiency

Although the risk of developing TB is generally high among pathologies involving immunodeficiency, the level of risk differs according to the pathology. In addition, caution is necessary when assessing risk due to the decreased infection diagnosis sensitivity of TSTs and IGRAs; however, many reports have stated that this decrease does not occur as easily with IGRAs as with TSTs²⁵⁾²⁶⁾. A comparison of lymphocyte counts and IGRA sensitivities yielded the following results: although sensitivity was reduced as lymphocyte count decrease in both QFT-G and T-SPOT, T-SPOT was less affected; sensitivity for TB patients with a lymphocyte count of $\leq 500/\mu\text{L}$ was 81% in T-SPOT but only 39% in QFT-G, a clear significant difference²⁷⁾. This result is believed to be because T-SPOT extracts peripheral lymphocytes from whole blood and adjusts them to a fixed number, whereas QFT-G is easily affected by the total lymphocyte count because it uses whole blood for its measurements.

i. HIV/AIDS

TB is the cause of roughly one-fourth of HIV deaths worldwide²⁸⁾. Various reports have stated that among individuals infected with TB, those infected with HIV have an approximately 10 times²⁹⁾, 20–37 times²⁸⁾, or 50–110 times¹¹⁾ greater risk of developing TB. Data have been amassed showing that LTBI treatment is effective for HIV-positive individuals and contributes to improved quality of life and survival rates³⁰⁾. Based on this situation, the WHO published a set of guidelines in 2011 for developing countries in which HIV is prevalent; these guidelines strongly encouraged the detection of TB and the use of INH preventive therapy for HIV-infected individuals¹⁰⁾.

In Japan, HIV prognosis and survival rates for HIV/TB coinfections have markedly improved since the introduction of powerful antiretroviral therapy³¹⁾³²⁾. Despite the improved prognosis, treatment for HIV/TB coinfection can easily produce side effects, which are believed to make treatment difficult in some cases³¹⁾. Therefore, it is desirable to incorporate the view recommended in the United States³³⁾ and perform LTBI treatment proactively.

In a meta-analysis that compared the use of T-SPOT and QFT-G for HIV-infected individuals, the pooled sensitivity of T-SPOT was 72%, slightly higher than the 61% for QFT-G. In data from high-income countries, while QFT-G results were indeterminate in a substantial number of cases in which CD4+T cell counts were lower than 200/ μL , indeterminate results did not occur with T-SPOT²⁶⁾.

ii. Hemodialysis for chronic renal failure, and kidney transplant recipients

The relative risk of developing active TB is 10–25 times higher for patients undergoing hemodialysis due to chronic renal failure^{11)34)–36)}, and 37 times higher for kidney transplant recipients³⁷⁾. TB often develops within 1 year following the introduction of dialysis³⁴⁾³⁶⁾. It is well known that reduced reactivity to TSTs sometimes occurs during chronic renal failure and hemodialysis; this reduced reactivity is believed to result in negative conversion in up to 50% of cases. Therefore, TB infection cannot be ruled out solely with a negative TST³⁸⁾. IGRAs, although not sufficiently evaluated, are reported to be capable of detecting TB with greater sensitivity than TSTs^{38)–40)}. Based on the above findings, LTBI treatment is considered for hemodialysis patients following IGRA and confirmation that TB has not developed in individuals suspected of being infected. However, due to the advancing age of dialysis patients in recent years, the patient's physical status and the possible manifestation of side effects must be sufficiently considered.

For kidney transplant recipients, immunosuppressants administered post-surgery may reduce the sensitivity of IGRA, and RFP may affect the transplanted kidney. In light of these possibilities, preoperative TB diagnosis is recommended, and LTBI treatment should be performed as necessary³⁸⁾.

iii. Recipients of other transplanted organs and stem cell transplants

TB may result as a complication of transplantation of other organs or stem cells. The risk of TB development in individuals who have received transplants is believed to be 20–74 times greater than that of the average person¹¹⁾. Treatment of TB that develops following a transplant is often difficult due to the interaction between anti-TB drugs and immunosuppressants⁴¹⁾. Therefore, IGRA is used to perform an infection diagnosis before transplantation, and LTBI treatment is performed for patients with positive IGRA results following confirmation that TB has not developed.

iv. Diabetes

The risk of TB development in individuals with diabetes is

considered to be 1.5–3.6 times greater than that of the average person¹¹⁾⁴²⁾⁴³⁾. In a meta-analysis of 13 studies, the relative risk was 3.11 (95% confidence interval: 2.27–4.26); however, in studies of individual cases, the odds ratio ranged 1.16–7.83⁴⁴⁾. The risk of developing TB is correlated with the level and duration of hyperglycemia; while there is no increased risk when hemoglobin A1c (HbA1c) is below 7, the risk triples when HbA1c is 7 or higher⁴⁵⁾. Moreover, the risk of developing TB is correlated with the severity of diabetes; whereas the risk in diabetes overall is 2.09, the risk for patients undergoing treatment is 2.60, while the risk for patients with 2 or more complications is 3.45 compared to patients without treated diabetes⁴⁶⁾. Therefore, before selecting a patient as a subject for LTBI treatment, suitable glycemic control is considered important.

Although there have been no recent intervention studies related to the utility of LTBI treatment for diabetes patients, LTBI treatment was observed to reduce TB development risk in past observational studies⁴²⁾. These observational studies do not provide sufficient evidence to support LTBI treatment for diabetes patients. However, as LTBI treatment is believed to be valid in other pathologies that cause immunosuppression, it is believed worthwhile to consider the use of LTBI treatment as necessary.

It has been reported that the diagnostic accuracy of IGRA are not affected in diabetes⁴⁷⁾⁴⁸⁾. Therefore, LTBI treatment is considered when diabetes control is difficult, the risk of TB development is considered high due to other overlapping factors, and the patient is infected with TB.

(3) Use of drugs with immunosuppressive effects

i. Biologics

The number of biologics has expanded in recent years, as has the list of diseases susceptible to them. The biologics sold in Japan are listed in Table 1. Regarding the risk of TB development due to the use of biologics, prospective studies are difficult due to the dearth of TB cases in Europe and the United States; therefore, calculations have been made using various data sources and aggregation methods. However, due to differences stemming from clinical pathologies and the biologics used, the risk varies widely according to the report, ranging 1.6–25.1⁴⁹⁾⁵⁰⁾. The time from administration to TB development depends on the drug; for example, the period is 17 weeks for infliximab versus 48 weeks for etanercept. The risk of TB development is 1.3–5.9 times higher with infliximab than with etanercept, while many reports have stated the risk with adalimumab is even higher than that with infliximab⁵⁰⁾. In a study that used a Swedish national database, the risk of TB development for rheumatoid arthritis patients who did not use TNF- α inhibitors from 1999 to 2001 was twice as high as that for the general population. Additionally, while risk among rheumatoid arthritis patients treated with TNF- α inhibitors from 1999 to 2004 was roughly 4 times higher than the risk among non-users, some cases were not reported; therefore,

the actual figure is considered even higher⁵¹⁾. In a case-control study as part of the French Research Axed on Tolerance of Biotherapies registry, the standardized incidence rate (SIR) was 12.2. Furthermore, there were large differences depending on the drug used; the SIR was 18.8 with infliximab, 29.3 with adalimumab, and 1.8 with etanercept⁵²⁾. The risk of TB development with tocilizumab is considered low⁵³⁾. Among 1945 cases in which disease-modifying anti-rheumatic drugs (DMARDs) were administered along with abatacept and 891 cases in which DMARDs were administered with golimumab, TB developed in only 1 case in both groups (however, nothing was stated regarding the performance or non-performance of LTBI treatment before the initiation of drug therapy)⁵⁴⁾. Based on the above findings, there is a clear high risk of TB development associated with infliximab and adalimumab, whereas the risk associated with etanercept is lower.

It was reported before DMARDs came into use that skin reactions such as those with TSTs were diminished in rheumatoid arthritis and other immune-related inflammatory diseases⁵⁵⁾. Furthermore, due to the frequent use of DMARDs in cases in which biologics are used, false negatives may occur in TSTs and IGRA^{56)–58)}. Regarding the use of biologics, the British Thoracic Society has recommended that in cases where immunosuppressants are already being used, TSTs are not helpful in diagnosing TB infection and therefore should not be used⁵⁶⁾. A collection of reports of TB screenings for patients with inflammatory diseases related to chronic immune problems has shown that many cases with positive results in IGRA (as many as 50%) yielded negative results in TSTs⁴⁹⁾⁵⁹⁾; therefore, IGRA is considered to have higher sensitivity than TSTs. However, reactivity is also believed to be reduced in IGRA, indicating the need to lower the threshold for a positive result⁶⁰⁾. In a report in which both QFT-G and T-SPOT were performed in screenings of patients using biologics, there was no significant difference in lymphocyte counts between the QFT-G–positive/T-SPOT–negative group and the QFT-G–negative/T-SPOT–positive group¹⁸⁾.

Based on the above findings, when assessing the appropriateness of biologics, the first step is to assess the subject's risk of TB infection based on their medical history. Next, chest radiography is performed; if active TB is suspected, a detailed examination is necessary for a definitive diagnosis. LTBI treatment is proactively considered if old pulmonary TB is suspected and the patient has no treatment history or no proper treatment has been administered. IGRA is used to diagnose infection when no abnormalities are observed on the chest radiograph; if infection is suspected, LTBI treatment is performed 3 weeks earlier to the initiation of the treatment using biologics. When using biologics, it is important to perform regular tests in response to the manifestation of serious side effects and to be able to respond rapidly to side effects that may develop suddenly. In order to do so, there should be cooperation with infectious disease specialists in medical care environments in which chest radiographs can be developed

immediately and studied by pulmonologists and radiologists to yield findings⁵⁶⁾⁵⁷⁾⁶¹⁾⁶²⁾.

ii. Corticosteroids

Administration of 15mg/day (or an equivalent dose) oral prednisolone for 1 month or longer has been established as a statistically evident risk factor for developing TB³⁾. One report found that the overall odds ratio of TB development for individuals using oral prednisolone was 4.9, while the odds ratios for those using less than 15 mg and those using more were 2.8 and 7.7, respectively⁶³⁾. In another report, among rheumatoid arthritis patients not using TNF- α inhibitors, the age- and sex-SIR of TB for patients using corticosteroids was 2.4 times higher than the rate for patients not using corticosteroids⁶⁴⁾.

The use of inhaled steroids has been reported to increase the risk of developing TB when oral steroids are not administered. In the case of particularly large doses ($\geq 1000 \mu\text{g/day}$ fluticasone), the risk of developing TB is double that of non-users of inhaled steroids. However, inhaled steroids do not increase risk any further when oral steroids are used⁶⁵⁾.

Administration of 10 mg/day oral prednisolone suppresses TST and QFT-G reactivity⁶³⁾; therefore, IGRA infection diagnoses should be performed before beginning treatment. When an equivalent dose or higher of corticosteroids is already being used, the necessity of LTBI treatment is assessed while considering that the sensitivity of IGRA may be reduced.

Based on the above findings, when corticosteroids are used, the necessity of LTBI treatment is examined while considering the route of administration, dose, the risk of developing TB due to factors other than corticosteroid use, and the risk of occurrence of side effects.

iii. Other immunosuppressants

For rheumatoid arthritis patients, the relative risk of developing TB is considered to be 2–16 times based on the effects of the disease itself and DMARDs⁵¹⁾⁵²⁾. Other reports have stated that in cases in which TNF- α inhibitors are not used and DMARDs are used, the age- and sex-SIR is 2⁶⁵⁾ or 3⁶⁶⁾. (The DMARDs in these studies included the following: methotrexate, hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, leflunomide, cyclosporine, cyclophosphamide, gold compounds, minocycline, and penicillamine.)

Therefore, IGRA is used to diagnose TB infection in patients using DMARDs when other risk factors are present; LTBI treatment is then considered if the result of the IGRA is positive.

(4) Other infections and TB development risk factors

i. Healed TB lesions in chest radiography

The relative risk for untreated old TB lesions is considered 6–19; this is the highest risk following advanced HIV infection and close contact with infectious TB¹¹⁾. For individuals with chest radiography findings of old TB (excluding individuals with only pleural adhesion images or calcification) who have not previously undergone anti-TB chemotherapy, a 24-

week regimen of INH is reported to reduce the incidence of TB development by 65%⁶⁷⁾; thus, LTBI treatment has been established as useful for untreated old pulmonary TB. On the other hand, in a recent estimation of TB development rates among infected individuals conducted in the American Southeast, risk is somewhat increased among individuals aged 50 years or older and those born in the United States; however, this risk is considerably lower than it was in the 1950's. This is inferred to be because TB treatment is now widespread, and because the number of individuals with untreated, old healed lesions has declined, mainly among the elderly⁶⁸⁾. In Japan, there are few untreated cases as well due to treatment with anti-TB drugs becoming widespread in the 1950's; very elderly people are inferred to account for a disproportionate number of untreated cases. Individuals already infected with TB, including those with old lesions on chest radiograph, are not subjects for LTBI treatment. Considering this and the possible manifestation of side effects, the number of potential subjects for proactive LTBI treatment among the elderly is inferred to be limited.

ii. Silicosis

In silicosis, which has a relative risk of 30, the risk of developing TB is extremely high¹¹⁾, although it has been reported that LTBI treatment can halve the risk⁶⁹⁾. However, the number of applicable cases is considered limited due to the recent decrease in silicosis occurrence and the aging of silicosis patients.

iii. Weight

Relative risk for underweight individuals (BMI $< 20 \text{ kg/m}^2$) is 2.8 compared to normal body weight individuals (BMI = $20\text{--}25 \text{ kg/m}^2$), while relative risk for overweight individuals (BMI $> 25 \text{ kg/m}^2$) is 0.5⁶³⁾. These values are considered equivalent to values in a study of United States Navy recruits; in this study, the risk of TB development for recruits whose weight was $\geq 15\%$ underweight from the standard weight for their height was double the risk for those of standard weight and triple the risk for overweight individuals³⁾. In a TBnet consensus statement, LTBI treatment is generally considered unnecessary for these individuals⁴⁹⁾. LTBI treatment is considered only in cases that also present with other risk factors.

iv. Smoking

Several types of recent epidemiologic studies (including meta-analyses) have reported active and passive smoking as an independent risk factor for TB; the relative risk for TB infection is 1.5–2 times, relative risk for TB development is 2–3 times, and the relative risk for severe symptoms (including lung cavities) and death due to TB is 1.5–3 times^{70)–72)}. Due to the large number of smokers, their attribution to TB development in the target population is considerable⁵⁶⁾, even in comparison to corticosteroid users, for whom relative risk is clearly high. Therefore, it is first important to promote measures to help smokers quit smoking. There has been discussion regarding a program to allow for proactive LTBI treatment for smokers who are unable to quit⁷¹⁾; consideration of such

intervention is considered necessary when examining LTBI treatment in cases in which other TB development risk factors are clearly present. LTBI patients must also be interviewed regarding smoking, and smokers must be given instructions for quitting smoking.

v. *Being from a high-prevalence country*

In developed countries such as the United States and countries in Europe, foreign-born individuals account for approximately half of all TB patients. In a survey of countries belonging to the Organisation for Economic Co-operation and Development (OECD), some method of screening for TB development is conducted in 25 of the 29 countries (86.2%) that responded; however, LTBI screening is conducted only in 16 of the 29 countries (55.2%). Many of these countries treat refugees, while regular immigrants are assigned low priority. In many of the countries, targets for treatment are children and young people who have high risk for developing the disease. There are major differences in prevalence among the target countries, which use different screening methods; for example, some countries use TSTs or IGRA, while other countries combine both methods⁷³⁾. For example, in the United Kingdom, TB screening is performed for new arrivals from countries where prevalence is more than 40 cases per 100,000 people per year; LTBI treatment is performed when a TST or IGRA result is positive (without a prior BCG vaccination) and active TB has been ruled out³⁷⁾. In a United States study, a model calculation was used to calculate the lifetime risk of developing TB; from a cost-effectiveness perspective, proactive LTBI screening is considered beneficial in the United States, regardless of time living in the country¹³⁾. Taking into account the prevalence situation in Japan, IGRA is performed for arrivals from high-prevalence countries (more than 100 cases per 100,000 people per year) when those people may have been infected recently and possess immunological problems; LTBI treatment is considered for those who test positive, while sufficiently considering the prospects of completing treatment. Treatment is considered more proactively for those with a high likelihood of causing secondary infections by developing TB; such individuals include overseas students, technical intern trainees, and those who live in groups.

vi. *Healthcare workers*

The risk of developing TB for healthcare workers in Japan, particularly nurses, differs according to the report based on age group, subjects, and calculation methods; however, prevalence is approximately 3–4 times higher than for average females of the same age group^{74)–79)}.

Our Prevention Committee established “Tuberculosis Infection Measures in Medical Facilities” in March 2010. Previously, a 2-step TST was conducted to establish a baseline for healthcare workers when they were employed; now, it is advised that the QFT-G result be used as a baseline. LTBI treatment is recommended for individuals with a positive QFT-G result in screening who are suspected of recent infection (generally, within the past 2 years)⁸⁰⁾. The reason for this

is twofold: TB development risk is low in cases where time has passed since infection; and the positive predictive value is not necessarily high due to the low existing TB infection rate among the younger generation, which comprises the majority of new healthcare workers (for example, when the infection rate is 1%, IGRA sensitivity is 90% and specificity is 98%, the positive predictive rate is slightly above 30%). LTBI treatment was not performed for 61 healthcare workers with positive results in a QFT-G test performed as a baseline; in a follow-up for 286 person-years, not a single healthcare worker developed TB⁸¹⁾. This result is considered to support the idea that treatment is not necessary for non-recent infections.

In QFT-G screening for healthcare workers and a follow-up observation, positive conversions were defined as changes from less than 0.35 IU/mL to 0.35 IU/mL or greater, with such individuals considered infected; however, because there were also cases in which this reaction value increased due to biological variations, the possibility was indicated that infection cannot be correctly assessed¹⁵⁾¹⁶⁾⁸²⁾. Therefore, there is also the view that a change from less than 0.35 IU/mL to 0.70 IU/mL or more is considered to indicate infection¹⁵⁾, while another view holds that values from 0.20 IU/mL to 0.70 IU/mL are indeterminate¹⁶⁾. These may be topics for future investigation.

3. *Actual application of treatment*

Based on the above discussion, we compiled the relative risks for various risk factors and LTBI treatment targets (relative to the absence of individual risk factors or relative to average people) in Table 2. Risk factors considered to require examination of proactive LTBI treatment (advisory level A, Table 2) are those with a relative risk of 4 or higher; these include HIV/AIDS, organ transplants (use of immunosuppressants), silicosis, hemodialysis due to chronic renal failure, recent infection (within the last 2 years), fibronodular shadows in chest radiographs (untreated old TB lesions), and the use of biologics. For the following factors (advisory level B, Table 2), the risk of TB development is somewhat high, and LTBI treatment is examined when these risk factors overlap: oral or inhaled corticosteroid use, use of other immunosuppressants, diabetes mellitus, being underweight, smoking, and gastrectomy. Regarding healthcare workers, while immunological statistics show that the risk for nurses is 3 times that of average females of the same age group, TB does not often develop in individuals with positive IGRA results. Therefore, healthcare workers may not need to be considered subjects for treatment if there is no possibility that they were infected recently.

4. *Topics for future investigation*

The selection of subjects for LTBI diagnosis and treatment require the examination of other items as described below:

(1) *Infection diagnosis methods*

As the number of studies related to IGRA continues to increase, new technical findings must be incorporated as necessary. In particular, there is still much research to be done

on diagnostic characteristics in immunosuppression and in children. In addition, the use of T-SPOT in Japan only began recently; therefore, data must be accumulated.

(2) TB infection and development risk

Much is still unknown regarding TB development risk in immunosuppression and the use of biologics and other drugs with immunosuppression effects.

(3) Consideration of subjects

The homeless and day laborers are socially high-risk groups; however, it is necessary to consider problems in the actual application of treatment, such as the possibility of actually conducting screening and ensuring that they take their medicine correctly. Additionally, as prevalence is high among inmates in correctional facilities, it is necessary to consider the possibility and usefulness of screening for them.

3. Treatment

1. Drugs and administration periods

In accordance with the standards for TB care⁸³⁾, INH is generally used for 6 or 9 months. When INH cannot be used, RFP is used for 4 or 6 months. The ratings and evidence for each treatment protocol based on the ATS/CDC joint statement are shown in Table 3³⁾. An administration period of 6 months refers to 180 administrations; individuals who frequently forget to take their medicine and can only take it for 150 days within that period are not counted in the 6-month administration period. Regarding immunosuppressed patients, some feel that a period of 6 to 9 months is too short; however, while some research papers recommend long-term administration, others do not.

(1) INH

a. Effects of INH for immunocompetent individuals

Through the use of INH, LTBI treatment has been reported to reduce the risk of progress to TB diseases in immunocompetent individuals (by anywhere from 25% to 92%, with an average of 2/3; however, restricting the results to individuals who take INH properly puts the effect at roughly 90%)⁸⁴⁾. Almost all of these are comparisons of a 12-month INH regimen to a control group. However, based on a review by Comstock⁸⁵⁾, which states that there is almost no difference when the INH treatment period is shortened to 9 months, 9 months is now considered the ideal period in the United States (A (II), Table 3)³⁾. A randomized controlled trial (RCT) concerning treatment periods shorter than 9 months showed, from comparisons with individuals for whom old shadows were observed on radiographs, that a 6-month regimen reduced the risk of TB by 65%, while a 12-month regimen reduced risk by 75%⁶⁷⁾. The recommended treatment period in the United Kingdom is 6 months³⁷⁾, whereas this option (B (I), Table 3) is considered inferior to the 9-month regimen in the United States³⁾.

b. Effects of INH for immunosuppressed individuals

The only existing RCTs were conducted with HIV-positive individuals. A 12-month INH regimen for TST-positive individuals reduced TB development by 83%, whereas a 6-month regimen reduced TB development by a maximum of 40–68%; in the United States, a 9-month regimen is recommended³⁾. In Botswana, where there is a markedly high prevalence of TB, a 36-month regimen was reported to be more effective than a 6-month regimen (incidence of 2.22 cases per 100 person-years versus 0.57 cases per 100 person-years among

Table 2 Risk factors among infected individuals for developing active TB

Risk factor	TB development risk*	Reference	Advisory level	Remarks
HIV/AIDS	50–170	11)	A	
Organ transplant (immunosuppressant use)	20–74	11)	A	Pre-transplantation LTBI treatment is desirable
Silicosis	30	11)	A	Caution necessary as patients age
Hemodialysis due to chronic renal failure	10–25	11)	A	Consider carefully with elderly patients
Recent infection (within 2 years)	15	11)	A	Positive individuals in contact investigations
Fibronodular shadows in chest radiographs (untreated old TB lesions)	6–19	11)	A	Consider carefully with elderly patients
Use of biologics	4.0	11)	A	Development risk varies according to drug
Oral corticosteroid use	2.8–7.7	63) 64)	B	Consider when dose is large and risk is high
Inhaled corticosteroid use	2.0	65)	B	Development risk increases with high doses
Use of other immunosuppressants	2–3	65) 66)	B	
Diabetes with poor glycemic control	1.5–3.6	11) 42) 43)	B	Risk is not high in favorable glycemic control
Being underweight	2–3	11)	B	
Smoking	1.5–3	70)–72)	B	
Gastrectomy	2–5	3)	B	
Being a healthcare worker	3–4	74)–79)	C	Treatment when recent infection is suspected

*TB development risk is the relative risk relative to an individual without the given risk factor

Advisory levels:

A: Proactive LTBI treatment is considered

B: LTBI treatment is considered when risk factors overlap

C: Consideration of treatment is not immediately necessary

Table 3 LTBI treatment protocols

Drug	Standard dose mg/[kg·day]	Maximum dose mg/[body·day]	Duration (mo)	Rating* (evidence)**	
				HIV –	HIV +
Isoniazid	5	300	9	A (II)	A (II)
Isoniazid	5	300	6	B (I)	C (I)
Rifampicin	10	600	4	B (II)	B (III)

*A=Preferred, B=Acceptable alternative, C=Offered when A and B cannot be given

**I=randomized clinical trial data, II=data from clinical trials that are not randomized or were conducted in other populations, III=expert opinion

Note: Ratings and evidence are from an ATS/CDC joint statement³⁾.

TST-positive individuals, respectively)⁸⁶⁾; this is considered a preventive effect against new infections and reinfections. On the other hand, in a study conducted in South Africa, no difference was reported between a 6-month regimen and a 5-year regimen (incidence of 1.9 cases per 100 person-years versus 1.4 cases per 100 person-years among TST-positive individuals, respectively)⁸⁷⁾. Experts have various opinions regarding the need for a longer regimen.

Regarding other immunosuppressed individuals, TB developed in 11 of the first 2000 cases in post-marketing surveillance of infliximab (which became commercially available in 2003). However, once the risk of developing TB became widely known, TB developed in only 3 cases out of 3000; LTBI treatment was not administered in any of these TB cases⁸⁸⁾. In Japan, where the risk of TB infection is not as high as in African countries, it is believed that there are no reasons supporting long-term LTBI treatment, even for immunosuppressed patients.

(2) RFP

a. Effects of RFP

In an anti-TB study conducted with silicosis patients in Hong Kong, a 3-month RFP regimen reduced the incidence of TB by 63%, a 6-month INH regimen reduced incidence by 48%, and a 3-month regimen of INH+RFP reduced incidence by 41%⁶⁹⁾. We were unable to find any reports concerning the effects of RFP on immunosuppressed patients.

b. Use of INH versus RFP

Although there is no major difference in the effects of RFP and INH, INH has long been used by many patients, and many reports have confirmed its safety⁸⁹⁾ and efficacy; therefore, INH is used preferentially in the United States, the United Kingdom, and Japan (RFP is used when INH cannot be used due to side effects or resistance). Reports also exist concerning the acquisition of resistance to both drugs⁹⁰⁾⁹¹⁾. However, treatment is shorter in INH resistance cases than in RFP resistance cases⁹²⁾, and INH resistance is considered easier to manage. Therefore, the current standards of TB care, which prioritize INH use, are considered valid. However, there was also a report of INH-associated deaths due to liver injury in the United States⁹³⁾; such deaths are seen particularly frequently among patients aged 35 years or older. In Japan as well, there are reports of more serious side effects due to INH as the target

age range for LTBI treatment expands. Although INH is cheaper in strictly monetary terms, RFP can be deemed more cost-effective when considering other costs⁹⁴⁾.

2. Irregular administration of treatment

There is no evidence regarding treatment duration when treatment is administered irregularly.

(1) Switching from INH to RFP

There is no standard recommendation nor evidence on the duration of treatment until now, if the LTBI is given with INH for some days, then the drug is changed to RFP and treatment was given for some days with RFP. This guidelines recommend as an expert opinion that the duration of INH treatment (days) divided by 180 plus the duration of RFP treatment (days) divided by 120 is to be one. Therefore, 90 days treatment of INH and 60 days treatment with RFP is enough.

(2) Returning to medical care following discontinuation of treatment, and irregular use of medication

It has been discussed in the United States that a decrease in the ratio of prescribed medication used leads to decreased effects. However, it has been reported that even with an administration rate of 40–59%, the incidence of TB was reduced by 52% when medication was used for 10 months (also, with an administration rate of 80%, TB incidence was reduced by 68%)⁸³⁾. Therefore, it would still be considered effective if 6 months' (180 days) worth of medicine can be used in the course of 1 year. Even in cases of irregular use of medication and discontinuation of treatment, re-administration is recommended when it appears possible to use a prescribed period's worth of medication within double that period. However, irregular use presents the risk of acquiring resistance⁹¹⁾; therefore, when there is a high possibility that the patient will discontinue medication again, treatment should be discontinued, and the patient should be followed up.

(3) The effects of desensitization therapy on the treatment period

In cases where desensitization therapy is administered, there is no evidence regarding whether the lower dose therapy period should be counted as the number of days of medication use. Therefore, only the number of days on which a normal dose

is taken is calculated.

3. Daily dose

INH: for adults, 5 mg/kg body weight; for children, 10 mg/kg, maximum 300 mg.

RFP: for adults, 10 mg/kg body weight; for children, 10–20 mg/kg, maximum 600 mg.

As a rule, both INH and RFP are administered once per day.

4. Contact with INH- and RFP-resistant TB

No studies demonstrate the efficacy of LTBI treatment for patients that cannot use INH or RFP due to multi-drug resistant TB or serious side effects of drugs. In cases where TB is susceptible to pyrazinamide (PZA), ethambutol (EB), or levofloxacin (LVFX), expert opinion in the CDC guidelines recommends follow-up observation or a 6-month or longer regimen of PZA+EB or PZA+LVFX for immunocompetent individuals; and a 12-month or longer regimen of PZA+EB or PZA+LVFX for HIV-positive individuals and other immunocompromised individuals³⁾. Our society's report only states what is recommended in the United States without making its own recommendation for a treatment regimen. In many cases of LTBI treatment failure (that is, when TB develops during treatment or after completion of treatment), TB develops while still susceptible to the drug being used, although resistance is sometimes acquired⁹¹⁾. In multi-drug resistant TB, the acquisition of resistance resulting from LTBI treatment may further reduce the possibility of healing. Therefore, one possible option is to conduct careful follow-up observation while immediately providing appropriate treatment in the event TB develops. LTBI treatment for individuals in contact with someone with multi-drug resistant TB should be administered by a doctor with much experience with multi-drug resistant TB and LTBI treatment.

5. Managing side effects

(1) INH

The serious side effects of INH include liver injury, peripheral neuropathy, and allergic reactions; in rare cases, the serious side effects may also include pneumonitis and myelosuppression. Of these, liver injury requires the anticipation of side effects through regular inspection and testing⁸⁹⁾⁹³⁾. On the other hand, peripheral neuropathy, allergic reactions, and pneumonitis are all mild⁹⁵⁾ and can be treated as they appear (peripheral neuropathy is treated with vitamin B₆; allergic reactions and pneumonitis are treated with steroids as necessary, or by suspending INH in serious cases). Serious liver injury is seen very rarely in children aged below 15 years in the United States; regular reviews of symptoms during consultations and the detection of symptoms in examinations, is considered sufficient. For individuals aged 15 years or older (particularly patients aged 35 years or older, as well as those aged 15–34 years) with a past history of liver injury, pregnant women, HIV-positive individuals, and heavy drinkers, regular

liver function tests are necessary when beginning treatment and when symptoms manifest. In the United States, where more serious side effects are observed than in Japan, baseline liver function tests are necessary for individuals with a past history of liver injury, pregnant women, HIV-positive individuals, and heavy drinkers, and subsequent testing is indicated only at the following times: occurrence of baseline abnormalities, manifestation of symptoms, pregnancy, and increased risk of other side effects³⁾.

Expert opinion regarding the frequency of regular testing is that there is no clear evidence. In the United States, serious cases of liver injury occur at various times after beginning treatment; this does not constitute evidence that tests can be performed less frequently after 2 months have passed. One proposal is to conduct testing once every 1–2 months during the overall medication administration period.

(2) RFP

The serious side effects of RFP include liver injury, allergic reactions, and influenza-like symptoms as a type of allergy; in rare cases, the serious side effects may also include pneumonitis and myelosuppression. Of these, liver injury, pneumonitis, and myelosuppression require the anticipation of side effects through regular inspection and testing. Regular liver function tests, kidney function tests, and blood tests are necessary when treatment is initiated and when symptoms manifest.

LTBI treatment is not conducted with RFP as often as with INH; therefore, there are even fewer findings regarding the frequency of tests. However, as with INH, one proposal is to conduct testing once every 1–2 months during the overall medication administration period.

6. Monitoring of TB development during treatment

There have been reports of clinical breakdown to TB diseases during LTBI treatment. Attention should be paid to the symptoms of TB diseases, including coughing and sputum for pulmonary TB; chest pain, fever, and respiratory distress for TB pleurisy; lymph node swelling for lymph node TB; high fever in miliary TB; and headaches and impaired consciousness for tuberculous meningitis. When these symptoms appear, the possibility of TB development must be kept in mind when performing examinations and tests, and this possibility must be sufficiently explained to the patient to ensure comprehension. Chest radiography is performed when beginning LTBI treatment, when symptoms manifest, and at the end of treatment.

7. Health education

Health education regarding the risk of side effects and developing TB, as well as the risks associated with discontinuing medication, is necessary. Delaying the diagnosis of side effects allows them to become more serious. In light of deaths due to liver injury in the United States, such side effects must be explained. In addition, irregular administration of medication

results in an increased risk of acquiring resistance⁹⁰⁾, while discontinuing treatment results in an increased risk of developing TB⁹⁶⁾. In addition to giving the patient educational materials and providing sufficient clarification, it is necessary to ask the patient whether he or she understood what was explained. Please feel free to use the explanation we have provided as a reference.

8. Medication adherence support

As Prevention Guidelines have been revised, LTBI has also become a target for DOTS (Directly Observed Treatment, Short-course). At a DOTS conference, it was decided that health centers would cooperate with medical care facilities to support patients in continuing treatment and to assess therapeutic outcomes. When beginning treatment, health education is conducted at a medical care facility, while a notification of infection and an application for public expenses for medical care are submitted to a health center. A medication adherence support plan is formulated at the health center when the patient applies for public expenses for medical care. Many health centers provide the patient with a DOTS medication adherence notebook when the patient visits the health center (some areas have different names for this notebook). Medical care facilities

that have a TB ward or otherwise treat many TB patients prepare their own medication adherence notebook (or may be provided with one by the local government). These medical care facilities cooperate with health centers in providing medication adherence support by entering information obtained at the facility in the patient's DOTS medication adherence notebook. In addition, many medical care facilities with many TB patients are believed to hold regular DOTS conferences with health centers; LTBI treatment is also included as a subject in these DOTS conferences as necessary. When patients are judged to have problems adhering to their medication during outpatient treatment or stop visiting the hospital, the hospital contacts the health center to assist the patient with continuing their medication.

9. Post-treatment risk of TB development, and approaches to follow-up observation

The risk of clinical TB after treatment of LTBI varies according to the accuracy of the LTBI diagnosis, individual TB development risk factors, and therapeutic effects; therefore, a categorical discussion is not possible. An example of a view of this risk is as follows. In the case of a new infection, assuming that the risk of developing TB within 2 years without

Reference material: "Explanation for patients (draft)" (INH administration)

Tests have shown that you are infected with TB. There is a possibility that you will develop TB in the future (this is called LTBI). Infected individuals can reduce the possibility of developing active TB by taking medicine to prevent the development of TB. It is therefore recommended that you take TB medication.

Being infected with TB means that your body harbors a bacterium called *Mycobacterium tuberculosis* (Mtb) and is reacting to it. This is not the same as developing active TB. Active TB refers to showing symptoms or abnormalities in bacterial tests such as radiographs or sputum tests. However, in your current state, you have not developed TB. Your body's status is normal, and you are not at risk for infecting others with Mtb.

Being infected does not mean that you will develop TB. However, there is a certain risk of developing TB, but this risk can be reduced by taking medication (unfortunately, this risk cannot be reduced to 0). Not all people in your situation develop TB, so it is recommended that you take medication. However, instead of taking medication, you can also have your status checked through hospital visits and radiography. If you develop TB, you need to realize it immediately, as you may be at risk for infecting others. Therefore, your status will be checked through regular hospital visits and radiographs.

The medication used in treatment is TB medication. Typically, 4 types of medication are used when treating active TB. However, for people like you, who are only infected and have not developed TB, only 1 type of medication is used.

The medication is administered for 6 months or more. By taking medication throughout this period, the risk of developing TB is reduced by about 2/3. In other words, if you have a

15% risk of developing TB without taking medication, then taking medication will reduce the risk to 5%.

Once you begin taking medication, you must take it every day. If you constantly stop and re-start taking the medication, it will not work well.

However, some people sometimes develop side effects to this medication. The possible side effects include liver problems and allergic reactions, but most people are able to continue their medication while watching out for side effects. Symptoms include loss of appetite due to liver problems. Allergic reactions include itchy rashes and fever. However, if you develop TB, you will have to take 4 types of medication (including the one taken for infection). The risk of side effects in this case is higher than the risk in infection treatment. Thus, even if you develop side effects to medication now, there would be a greater risk of side effects due to medication for active TB (which may develop if you do not take medication now). Therefore, it is recommended that you take medication because it is considered advantageous to do so. If side effects do occur and you experience symptoms such as loss of appetite, fever, rash, numbness in your hands or arms, difficulty breathing, or increased coughing, contact the hospital or clinic and make an outpatient visit. Side effects can be handled through examinations and tests.

LTBI treatment incurs medical expenses, but you can apply at a health center to receive assistance in the form of public expenses, which can reduce the amount you pay out-of-pocket. In addition, a public health nurse at the health center will assist you so that you remember to take your medication. Therefore, the hospital or clinic will contact the health center and ask you to consult with a public health nurse.

treatment of LTBI is 10% and that LTBI treatment prevents TB development 60–70% of the time, the risk after treatment of LTBI will be 3–4%. Regarding follow-up observation, individuals who have completed LTBI treatment are subsequently registered as “recovered tuberculosis patients” at a health center for 2 years in accordance with the Infectious Diseases Control Law; during that period, these individuals are followed-up every 6 months to confirm that they have not developed TB.

10. LTBI retreatment

No reports have stated that retreatment is effective for individuals with a history of anti-TB drug use, while it has been reported that retreatment had no effect in immunocompetent hosts⁸³). However, retreatment can be considered in certain cases, such as in the following example: in the first LTBI treatment regimen, there was insufficient evidence for an LTBI diagnosis due to the use of a TST; therefore, it is highly possible that it was not a true infection, whereas the patient is now thought to be clearly infected due to IGRA result and contact with an infectious individual. In other words, the first LTBI treatment regimen was meaningless because the person was not actually being infected, whereas now, LTBI treatment is considered effective because the person being truly and newly infected. Additionally, there have been cases where LTBI treatment or TB treatment was administered to the patient as a contact, but retreatment is debated due to the patient subsequently becoming immunosuppressed. Although retreatment cannot be strongly recommended in such cases due to lack of evidence, it can be considered if the risk of developing TB is extremely high.

11. Future topics related to treatment

INH+RFP and INH+rifapentine are not currently accepted as LTBI treatment drugs in Japan. The effect of INH+RFP, which is considered equivalent to that of INH standard therapy⁹⁷), is stated in the British NICE guideline³⁷). INH+rifapentine is recognized as an LTBI treatment regimen in the United States based on reports of its effectiveness⁹⁸); it is administered once a week for 3 months, a total of 12 times²³). Unlike previous forms of LTBI treatment, the medication is administered only 12 times, which permits easy direct observation. Although there is no evidence for these regimens in Japan, they are used internationally; therefore, it is conceivable that they will be considered for use in Japan in the future.

4. Related systems

TB is defined as a category 2 infectious disease by the Infectious Diseases Control Law (hereafter “IDCL”). The law describes systems for notification, registration and patient management and health centers, medication adherence support, and public expenses at the time of TB development as detailed below.

(1) Notification (IDCL Article 12)

A doctor who diagnoses a TB patient, a TB carrier with no symptoms, or someone suspected of TB infection is required to notify the prefectural governor through a nearby health center with the patient’s name, age, and any other required information. A health center that receives a notification concerning a patient living outside its jurisdiction must report to the health center with jurisdiction over that patient according to IDCL Article 53-10. Although LTBI is not a suspected symptom or finding of TB development in the notification standards⁵), the fact that the individual is infected requires them to receive treatment and requires notification that they are a TB carrier with no symptoms under the IDCL. When making a notification, a TST or QFT must be used to test for infection. However, a negative test result does not preclude a doctor from making a diagnosis of LTBI as an overall assessment.

(2) Registration (IDCL Article 53-12) and close examination (IDCL Article 53-13)

Health centers register required information regarding patients for whom notifications have been made (including LTBI patients) and recovered TB patients. A recovered TB patient is defined based on IDCL Enforcement Regulation Article 27-7 as an individual who has been recognized within the past 2 years as not requiring TB care but has a marked risk of redeveloping TB. Health center directors are required to ascertain the conditions of registered individuals (current and recovered TB patients) at least once every 6 months; this includes inquiring at the medical care facility conducting follow-up observation, as well as performing chest radiographs and other tests as necessary. The medical care facility and the health center must coordinate their cooperation to avoid problems such as repeating tests⁹⁹).

(3) Instruction during visits and medication adherence support (IDCL Articles 53-14 and 53-15)

Based on patient notifications, health centers instruct patients regarding therapy requirements, particularly proper medication adherence, through public health nurse visits or contact. The IDCL also requires instruction on proper medication adherence to be provided by doctors who prescribe anti-TB drugs. The “Standards for Tuberculosis Care”⁸³) state that “For patients currently undergoing treatment, sufficient instruction shall be conducted so that the patient properly adheres to their prescribed medication based on a support plan drafted in cooperation with the health center.” Previously, only smear-positive TB patients were designated targets in the Japanese version of the DOTS strategy. However, in accordance with a notice¹⁰⁰) issued in October 2011, all TB patients, including LTBI patients, are now included as targets.

(4) Public expenses (IDCL Article 37-2)

TB patients can apply for public expenses for medical care at a designated TB care facility. Pending approval in a review

by an infectious disease examination council at the health center, the patient's copayment is reduced. Medical care for which public expenses are paid includes therapy that conforms to medical care standards, chest radiography, CT, and tests to check for side effects; LTBI treatment was included in August 2007⁶⁾. The scope of public expenses extends to medical care administered after a patient notification has been submitted to a health center and a public expenses application has been received. However, this period can be retroactive to an earlier date due to unavoidable circumstances, such as the time required for the application to be mailed. Therefore, the scope of public expenses effectively extends to medical care performed after a definitive diagnosis has been made.

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