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**Original Article**

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**EVALUATION USING QFT-2G/TBGL/LAM IN THE PATIENTS  
WITH OSTEOARTICULAR TUBERCULOSIS OF POST-TREATMENT PERIOD**

Kazutaka IZAWA

**Abstract** [Purpose] To evaluate results of QFT-2G/TBGL/LAM in patients who had been completed the antituberculosis treatment for osteoarticular tuberculosis with various periods after the completion of the treatment.

[Materials and methods] Fifty-five patients who had been completed the antituberculosis treatment for osteoarticular tuberculosis at least one year after the completion of treatment were evaluated using QFT-2G/TBGL/LAM tests. Forty patients with spinal tuberculosis and 15 patients with articular tuberculosis were included. The patients with the period after the completion of the treatment less than 4 years were classified as short-term group (33 patients) and those with the period not less than 4 years were classified as mid-long-term group (22 patients). The results of the tests were compared between the two groups.

[Results] The result of QFT-2G test was positive in 60.6% of the patients in short-term group while 45.5% in mid-long-term group ( $p=0.12$ ). On the other hand, the result of TBGL test was positive in 75.8% of the patients in short-term group whereas 22.7% in mid-long-term group ( $p=0.0001$ ) and the result of LAM test was positive in 90.9% of the patients in short-term group whereas 63.6% in mid-long-term group ( $p=$

0.01), both of these tests showed significantly lower positive rate in mid-long-term group. There was no significant difference in the comparisons between patient groups with/without pulmonary tuberculosis as well as with/without surgical treatment.

[Conclusion] The patients with a history of osteoarticular tuberculosis tend to show positive results of QFT-2G test for a prolonged period, whereas significantly less positive results of TBGL/LAM tests in mid-long-term.

**Key words:** Osteoarticular tuberculosis, QuantiFERON®TB-2G, Tuberculous glycolipids (TBGL), Lipoarabinomannan (LAM), Mid-long-term follow-up

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## Original Article

## STUDY ON PULMONARY LESIONS IN WHICH NONTUBERCULOUS MYCOBACTERIA WERE DETECTED BY PERCUTANEOUS ASPIRATION

—A Proposal to Add “Culture Positivity of Percutaneous Aspiration Material” to the Bacteriological Diagnostic Criteria of Pulmonary Nontuberculous Mycobacterial Diseases—

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**Abstract** [Objectives] “Culture positivity of percutaneous aspiration material” is not included in the current bacteriological criteria for diagnosis of pulmonary nontuberculous mycobacterial (NTM) diseases, which were published by the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) in 2007 or those released by the Japanese Society for Tuberculosis in 2008. However, percutaneous aspiration is a reliable technique for the detection of causative microorganisms isolated from the focus of infection. We discuss the benefits of including positive culture of percutaneous aspiration material in the bacteriological diagnostic criteria of pulmonary NTM diseases.

[Methods] We reviewed the radiological images and clinical courses of pulmonary diseases in which NTM cultures were obtained from percutaneously aspirated materials at our hospital from 1991 to 2011. Aspiration was carried out under local anesthesia, usually with fluoroscopic guidance. After percutaneous insertion of a 22-gauge needle attached to a 20-mL syringe containing about 3 mL of saline, the lesion specimen was withdrawn together with the saline. After the needle was pulled out, the aspirated material and saline were transferred to test tubes for cytological and microbiological examinations. In patients with thin-walled cavitory lesions, saline was injected into the cavity and then aspirated.

[Results] Percutaneous aspiration was performed in 2,742 patients and NTM disease was detected in 51 patients. Of these 51 patients, 12 had solitary nodular lesions, and in many of these patients, no NTM bacilli could be detected in the sputa or bronchial washing specimens. *Mycobacterium avium* was identified in 10 of the 12 cases. Four of these 10 patients were

followed up after their diagnosis without any treatment: 3 showed spontaneous reduction in lesion size, while 1 patient’s condition remained unchanged. Four of the remaining 6 cases were treated with anti-NTM medications, and lesion size reduced in 2 cases, while no change or deterioration was seen in the other 2. Aspiration from solitary small cavitory lesions showed a relatively high number of NTM colonies. Pneumothorax was the only complication of the aspiration procedure.

[Discussion] If the diagnostic criteria for pulmonary NTM diseases include positive culture in percutaneous aspiration material, the diagnosis of solitary nodular NTM lesions would become easier; at present, these lesions are often diagnosed only upon surgical resection. Further, clinical studies on the possibility of spontaneous shrinkage of the solitary lesion and the value of its medical treatment would be promoted. Aspiration can easily differentiate NTM disease from pulmonary abscess or fungal infection in patients with a solitary lesion or small cavity.

**Key words:** Pulmonary nontuberculous mycobacterial disease, Percutaneous aspiration, Diagnostic criteria, Solitary nodular lesion, Fibrocavitary lesion

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CLINICAL EVALUATION OF A LINE PROBE ASSAY KIT FOR  
THE IDENTIFICATION OF *MYCOBACTERIUM* SPECIES AND DETECTION OF  
DRUG-RESISTANT *MYCOBACTERIUM TUBERCULOSIS*

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Generally, drug susceptibility testing takes more than 3–4 weeks after the initial cultivation. There is an urgent need to identify methods that can rapidly detect both the presence of *Mycobacterium tuberculosis* and the status of drug resistance.

[Purpose] This study was aimed at evaluating the line probe assay (LiPA; Nipro Co.), for the identification of *Mycobacterium* species and detection of mutations associated with anti-tuberculous drugs.

[Results] We found that LiPA enabled the rapid identification of *M.tuberculosis*, *M.avium*, *M.intracellulare*, and *M.kansasii*. When the results of the LiPA and conventional drug susceptibility tests were compared, there was no difference in the susceptibility to rifampicin, pyrazinamide, and levofloxacin; however, there was a difference in the susceptibility to isoniazid.

[Conclusion] Thus, LiPA can be used for the rapid identification of *Mycobacterium* species and the determination of susceptibility to drugs, which can help in the early initiation of appropriate treatment, leading to a reduction in infectiousness.

**Key words:** Multidrug-resistant *Mycobacterium tuberculosis*, Rapid diagnosis, Line probe assay

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## COMPARISON OF DRUG-INDUCED HEPATITIS OCCURRING IN ELDERLY AND YOUNGER PATIENTS DURING ANTI-TUBERCULOSIS TREATMENT WITH A REGIMEN INCLUDING PYRAZINAMIDE

<sup>1</sup>Naoki MIYAZAWA, <sup>1</sup>Nobuyuki HORITA, <sup>2</sup>Koji TOMARU, <sup>2</sup>Toshinori TSUKAHARA, <sup>2</sup>Ryohei TAKAHASHI, <sup>2</sup>Masahiro SASAKI, and <sup>3</sup>Yoshiaki ISHIGATSUBO

**Abstract** [Background] In Japan, tuberculosis (TB) patients aged over 80 years are usually treated with a regimen not including pyrazinamide (PZA) because of the risk of drug-induced hepatitis.

[Purposes] The purpose of this study was to investigate the occurrence of drug-induced hepatitis in TB patients over 80 years of age, who are treated with a regimen including PZA, and compare the findings with those of younger patients.

[Methods] Thirty-six patients with pulmonary tuberculosis, who were admitted to Yokohama City University Hospital between June 2011 and March 2012 were included. They were treated with isoniazid, rifampicin, ethambutol, and PZA and had their liver function assessed once a week for 2 months.

[Results] Hepatitis occurred in 4 of 28 (14.3%) patients aged under 80 years and in 1 of 8 (12.5%) patients aged over 80 years.

[Conclusion] There was no difference in the frequency of drug-induced hepatitis between patients aged under and over

80 years. We conclude that elderly patients aged over 80 years should be treated with a short course regimen that includes PZA.

**Key words:** Elderly patient, Anti-tuberculosis drug, Pyrazinamide, Drug-induced hepatitis, Short course chemotherapy

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## INTERPRETING “EQUIVOCAL” RESULTS OBTAINED FROM THE QUANTIFERON®-TB GOLD IN-TUBE TEST IN CONTACT INVESTIGATIONS

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[Methods] The participants of the contact examinations were assessed by the QFT-GIT test after 2 to 4 months from the last contact with smear-positive tuberculosis patients. The study was conducted between April 2011 and March 2012. We enrolled 79 contact participants whose QFT-GIT tests produced equivocal results.

[Results] The average age of the enrolled contacts was 35.9 years and the average interval from the last contact to the first QFT-GIT test was 85.4 days (range 62–118 days). The second QFT-GIT test produced negative results in 42 (53%) participants, equivocal results in 28 (35%), and positive results in 9 (11%). These 9 positive contacts belonged to the group of contacts with an index case whose QFT-GIT positive rate was more than 15%. The contacts belonging to groups with a QFT positive rate higher than 15% in the initial test had significantly higher QFT positive rates in the follow-up test than those belonging to groups with lower initial QFT positive rates ( $p=0.011$ ).

[Conclusions] After retesting contacts with initially equivocal QFT results, 65% demonstrated either negative or positive results. If a contact’s second QFT-GIT test is positive, it is highly probable that he/she is infected with tuberculosis and adequate treatment for latent TB infection is indicated. Thus far, no guidelines have been established for the management of contacts with equivocal results by the QFT-GIT test; therefore, further investigations and discussions are mandatory.

**Key words:** QuantiFERON®-TB Gold In-Tube, Equivocal of QFT, Serial testing, Contact investigation, Latent tuberculosis infection, Timing of examination

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**Case Report**

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**A CASE OF PULMONARY TUBERCULOSIS IN WHICH  
DIAGNOSIS WAS DELAYED BECAUSE OF PRIOR TREATMENT WITH  
FLUOROQUINOLONE AND METRONIDAZOLE**

<sup>1</sup>Shinichiro MORIOKA, <sup>2</sup>Ryogo EMA, <sup>3</sup>Aki SAKURAI, <sup>1</sup>Kazuhiro TOMITA,  
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**Abstract** We report the case of a patient with pulmonary tuberculosis, whose diagnosis was delayed because of prior treatment with fluoroquinolone and metronidazole. A 35-year-old woman developed productive cough, fever, and back pain, which lasted for 3 weeks before admission to hospital. She had been diagnosed with lower respiratory infection and was treated with garenoxacin mesilate hydrate for 7 days before admission. As her symptoms did not improve, she was referred to our hospital for further evaluation. A chest computed tomography scan revealed confluent consolidation in the right lower lung, predominantly in segment 7, and lung abscess was initially suspected. Since chemotherapy with ceftriaxone and minomycin did not reduce her symptoms, metronidazole was added on day 4. Her symptoms improved dramatically and she was discharged on day 15. Metronidazole was given for a total of 3 weeks, and 2 weeks after discontinuation of metronidazole, she presented with recurrent chest pain and was diagnosed with active pulmonary tuberculosis. In addition to the atypical imaging findings in this patient, the use of chemotherapeutics such as garenoxacin mesilate hydrate and metronidazole,

which have anti-tuberculosis effects, meant that the diagnosis of tuberculosis was complicated and hence delayed. We should keep in mind that some general chemotherapy agents, including linezolid, also have anti-tuberculosis effects and may cause similar problems with diagnosis.

**Key words:** Metronidazole, Fluoroquinolones, Pulmonary tuberculosis, Lung abscess

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## TUBERCULOSIS ANNUAL REPORT 2010

### — (8) Treatment of Tuberculosis—1 —

Tuberculosis Surveillance Center (TSC), RIT, JATA

**Abstract** The standard treatment of tuberculosis (TB) is the key to its control. Here, we report statistics relating to treatment history and first-line anti-TB therapy in the year 2010.

The frequency of retreatment among newly notified TB patients might be partly an indicator of previous insufficient treatment. In 2010, 23,261 TB patients were newly notified. Of these, 1,762 cases were reported as having had previous TB treatment. The proportion of retreatment among newly notified cases was 7.7%, excluding those with an unknown treatment history. Regarding the year of previous treatment, more cases had undergone prior anti-TB therapy in 2009 (n = 197).

As for the initial treatment regimen, a combination of isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA), and ethambutol (EB) or streptomycin (SM) is recommended by the Japanese Society for Tuberculosis. This regimen was initially used in 80.0% of all TB patients aged 15–79 years, excluding

those cases with an unknown treatment regimen. Of the 14,922 cases who started a TB treatment regimen including PZA and completed TB treatment by the end of 2010, 10.0% could not complete the full 2-month course of PZA.

**Key words:** Tuberculosis, Age, Treatment history, First-line treatment, Retreatment, Regimen, Pyrazinamide

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which have anti-tuberculosis effects, meant that the diagnosis of tuberculosis was complicated and hence delayed. We should keep in mind that some general chemotherapy agents, including linezolid, also have anti-tuberculosis effects and may cause similar problems with diagnosis.

**Key words:** Metronidazole, Fluoroquinolones, Pulmonary tuberculosis, Lung abscess

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## TUBERCULOSIS ANNUAL REPORT 2010

### — (8) Treatment of Tuberculosis—1 —

Tuberculosis Surveillance Center (TSC), RIT, JATA

**Abstract** The standard treatment of tuberculosis (TB) is the key to its control. Here, we report statistics relating to treatment history and first-line anti-TB therapy in the year 2010.

The frequency of retreatment among newly notified TB patients might be partly an indicator of previous insufficient treatment. In 2010, 23,261 TB patients were newly notified. Of these, 1,762 cases were reported as having had previous TB treatment. The proportion of retreatment among newly notified cases was 7.7%, excluding those with an unknown treatment history. Regarding the year of previous treatment, more cases had undergone prior anti-TB therapy in 2009 (n = 197).

As for the initial treatment regimen, a combination of isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA), and ethambutol (EB) or streptomycin (SM) is recommended by the Japanese Society for Tuberculosis. This regimen was initially used in 80.0% of all TB patients aged 15–79 years, excluding

those cases with an unknown treatment regimen. Of the 14,922 cases who started a TB treatment regimen including PZA and completed TB treatment by the end of 2010, 10.0% could not complete the full 2-month course of PZA.

**Key words:** Tuberculosis, Age, Treatment history, First-line treatment, Retreatment, Regimen, Pyrazinamide

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HEALTH EXAMINATION IN FUTURE  
AT THE ERA OF LOW TUBERCULOSIS INCIDENCE  
—From Contacts Examination toward Active Epidemiological Studies—

Chairpersons: <sup>1</sup>Hideo MAEDA and <sup>2</sup>Chika SHIRAI

**Abstract** Japan is still “intermediate burden” country as medium-incidence of tuberculosis (TB). But the incidence of TB varies by public health units. The priority for TB control would be lowering in the areas where the incidence of TB is relatively low. In addition, younger age groups get low prevalence of TB infection than elderly persons. As a result, fewer experiences for TB diagnosis and treatment in the hospital and the medical facility would cause the delay in the detection of TB patients which eventually cause outbreaks. Although there are differences in population density and population mobility between urban and rural areas, the socially economic vulnerable patients and foreign patients are the common risks. Any public health units’ policies of TB should correspond to the individual situation. At the era of low tuberculosis incidence, the infection risk is to be “From ubiquitous to the uneven distribution”. This makes TB detection much more difficult.

At this symposium, each speaker presented the case for

actually experienced with QFT test and/or VNTR analysis. They mainly focused on the paradigm shift in TB control which is indispensable for resolving the gaps in regional differences and the differences in diagnostic capability. Although the cases in this symposium were not for the low incidence situation, the pioneering approaches presented here would boost the future application of QFT and VNTR analysis nationwide. The discussions also partially covered the technical infrastructure for molecular epidemiology which covers the whole country. By making full use of QFT test and VNTR analysis as a contact screening tool, we can appropriately understand the risk of TB infection in the region from a buildup of bacteria and patient information. Now is the time to prepare for. Active surveillance of TB by this way would clarify the risk of the disease and lead to the advocacy essential for the resolution.

1. Current situation and challenge of contact survey by using QFT test in Tokyo: Hideo MAEDA (Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government)

2. Contact investigation of a tuberculosis outbreak: Kenichi MIYAMOTO (Takaido Community Health Center)

We have experienced a TB outbreak in integrated junior and senior high school in Tokyo. Index patient was a student with persistent respiratory symptoms for six months before diagnosis of sputum smear-positive TB. Public health center started contact investigation immediately. QFT-positive rates were high in close contacts, especially in classmates. Additionally, a student outside of contact investigation was diagnosed as TB and considered to be infected from the first patient by VNTR analysis. Therefore, public health center expanded QFT-tests to all students and teachers in this school. Finally, 9 students and 2 teachers in this school were diagnosed as sputum smear-negative TB by contact investigation.

3. Utilization of molecular epidemiological procedure in contact investigation in Kyoto City: Masahiro ITO (Public Health Center of Kyoto City)

Molecular epidemiological procedure using VNTR analysis has been used for contact investigation of tuberculosis since January 2011 in Kyoto City. One hundred forty four strains of *Mycobacterium tuberculosis* from patients with tuberculosis were investigated and 130 strains were fully analyzed. Fourteen clusters were found and the number of strains included in the cluster was ranged from two to 11. Epidemiological relationship between patients in one cluster was found, however, significant relationship in another clusters was not demonstrated. It was suggested that VNTR analysis is useful for molecular epidemiological analysis of tuberculosis.

4. The population based molecular epidemiological studies and QFT test in a contact examination: Riyo FUJIYAMA, Keisuke MATSUBAYASHI, Setsuko MIZUSHIRI, Junko

HIGUCHI, Chika SHIRAI, Yuko KATAGAMI, Mieko CHIHARA, Akihiro IJICHI (Kobe City Public Health Center), Kentaro ARIKAWA, Noriko NAKANISHI, Tomotada IWAMOTO (Kobe Institute of Health)

The population based molecular epidemiological studies should be made good use of contacts examination. In future, we expect the tuberculosis molecular epidemiological study improve search for the process of tuberculosis infection.

The QFT positive rates correlated well with closeness of contact. QFT test is considered useful for diagnosing tuberculosis infection. However, in the judgment of tuberculosis infection, we should consider the total result of contact investigation not only QFT test but also the contact situation.

5. Insights into the TB epidemiology through population based molecular epidemiological studies: Tomotada IWAMOTO (Kobe Institute of Health)

The population based molecular epidemiological studies unveiled the transmission dynamics of tuberculosis at bacterial clone level. This provides scientific evidences for achieving better TB control programs. In the advanced stage of the tuberculosis molecular epidemiological study, we expect to change the current geno-typing based molecular epidemiology to whole genome-typing based molecular epidemiology on the basis of the rapid innovation of next-generation sequencing technology.

**Key words:** Contacts examination, QFT test, VNTR analysis, Low-incidence

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—————The 87th Annual Meeting Symposium—————

## BIOLOGICS AND MYCOBACTERIAL DISEASES

Chairpersons: <sup>1</sup>Kazunari TSUYUGUCHI and <sup>2</sup>Tomoshige MATSUMOTO

**Abstract** Various biologics such as TNF-alpha inhibitor or IL-6 inhibitor are now widely used for treatment of rheumatoid arthritis. Many reports suggested that one of the major issues is high risk of developing tuberculosis (TB) associated with using these agents, which is especially important in Japan where tuberculosis still remains endemic. Another concern is the risk of development of nontuberculous mycobacterial (NTM) diseases and we have only scanty information about it. The purpose of this symposium is to elucidate the role of biologics in the development of mycobacterial diseases and to establish the strategy to control them.

First, Dr. Tohma showed the epidemiologic data of TB risks associated with using biologics calculated from the clinical database on National Database of Rheumatic Diseases by iR-net in Japan. He estimated TB risks in rheumatoid arthritis (RA) patients to be about four times higher compared with general populations and to become even higher by using biologics. He also pointed out a low rate of implementation of QuantiFERON test (QFT) as screening test for TB infection.

Next, Dr. Tokuda discussed the issue of NTM disease associated with using biologics. He suggested the airway disease in RA patients might play some role in the development of NTM disease, which may conversely lead to overdiagnosis of NTM disease in RA patients. He suggested that NTM disease should not be uniformly considered a contraindication to treatment with biologics, considering from the results of recent multicenter study showing relatively favorable outcome of NTM patients receiving biologics.

Patients with latent tuberculosis infection (LTBI) should receive LTBI treatment before starting biologics. Dr. Kato, a chairperson of the Prevention Committee of the Japanese Society for Tuberculosis, proposed a new LTBI guideline including active implementation of LTBI treatment, introducing interferon gamma release assay, and appropriate selection of persons at high risk for developing TB.

Lastly, Dr. Matsumoto stressed the risk of discontinuing TNF-alpha inhibitor during treatment for tuberculosis. He showed from his clinical experience that TNF-alpha inhibitor can be safely used in active TB patient receiving effective antituberculosis chemotherapy and it is even more effective for prevention of paradoxical response.

Active discussion was done about the four topics, including the matter beyond present guidelines. We hope these discussions will form the basis for the establishment of new guideline for the management of mycobacterial disease when using immunosuppressive agents including biologics.

1. The risk of developing tuberculosis (TB) and situations of

screening for TB risk at administration of biologics—the case of rheumatoid arthritis: Shigeto TOHMA (Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital)

We calculated the standardized incidence ratio (SIR) of TB from the clinical data on National Database of Rheumatic Diseases by iR-net in Japan (*NinJa*) and compared with the SIR of TB from the data of the post-marketing surveillances of five biologics. Among 43584 patient-years, forty patients developed TB. The SIR of TB in *NinJa* was 4.34 (95%CI: 3.00–5.69). According to the post-marketing surveillances of 5 biologics, the SIR of TB were 3.62–34.4. The incidence of TB in patients with RA was higher than general population in Japan, and was increased more by some biologics. We have to recognize the risk of TB when we start biologics therapy to patients with RA. Although the frequency of implementation of QuantiFERON test (QFT) had gradually increased, it was still limited to 41%. In order to predict the risk of developing TB and to prevent TB, it might be better to check all RA patients by QFT at the time of biologics administration.

2. Biologics and nontuberculous mycobacterial diseases: Hitoshi TOKUDA (Social Insurance Central General Hospital)

Several topics about the relationship between RA and nontuberculous mycobacterial (NTM) diseases were discussed, which is still poorly understood. It is well known that airway diseases often accompany RA, which may be considered as a possible etiology for development of NTM diseases, but conversely it may lead to overdiagnosis of NTM disease. Next, we evaluated justification for the contraindication of biologics in patients with NTM diseases. Recent multicenter study showed that prognosis of patients developing NTM diseases during treatment with biologics were not always poor, which throws doubt on uniform prohibition of biologics in NTM diseases.

3. Future guideline for treating latent tuberculosis infection: Seiya KATO (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

The Japanese Society for Tuberculosis issued a joint statement on chemoprophylaxis with the Japan College of Rheumatology in 2004. However, issues and challenges due to changing circumstance indicate application of interferon gamma release assay (IGRA), increased variety and indication of biologics, dissemination of knowledge on strategy and system for latent tuberculosis infection (LTBI), etc. Future guideline should include 1) promoting LTBI treatment to achieve low incidence, 2) updated information on IGRAs, 3) treatment strategy and target: contact to infectious cases,



immunosuppressive cases (especially HIV and patients treated with biologics), high risk groups, etc. 4) fundamental information on tuberculosis control strategies, especially DOTS.

4. Therapy for RA and tuberculosis in patients with RA and TB activated by anti-TNF treatment: Tomoshige MATSUMOTO (Osaka Prefectural Medical Center for Respiratory and Allergic Diseases)

Biologics targeting TNF, including infliximab, have brought about a paradigm shift in the treatment of rheumatoid arthritis (RA). In 2001, tuberculosis, an ancient and also modern scourge, became spotlighted again, because Keane reported in *the New England Journal of Medicine* that infliximab administration induced reactivation of tuberculosis. How should we treat RA after we successfully treated tuberculosis? Decisions regarding the treatment of patients with refractory RA in the setting of active tuberculosis remain difficult. We successfully treated RA in patients with tuberculosis by

anti-TNF therapy. These demonstrate that anti-TNF therapy can be considered for patients with refractory RA who have tuberculosis and in whom antituberculosis therapy can be maintained.

**Key words:** Biologics, Rheumatoid arthritis, Tuberculosis, Nontuberculous mycobacteriosis (NTM), Latent tuberculosis infection (LTBI)

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