MYCOBACTERIOSIS ASSOCIATED WITH ADMINISTRATION OF BIOLOGICS

Akira WATANABE

Abstract In recent years, administration of biologics for immunologic inflammatory diseases, particularly rheumatoid arthritis, has increased obviously. These substances have dramatic effects, but complications of various infections such as tuberculosis are increasing. Biologics is an antonym for synthetic products (compounds), which are the most common type of pharmaceuticals, made by bioengineering materials derived from living organisms including humans. As concerns preparations which inhibit TNF-α that constitutes the basis of human immunity to tuberculosis, there was a fear that there might be an increase in tuberculosis in Japan, where many people have a history of tuberculosis infection due to past epidemics. However, it was confirmed in post-marketing all-case surveillance in Japan that tuberculosis can be prevented by screening for latent tuberculosis infection (LTBI) in the target patient population, and administering an anti-tuberculosis drug to patients with the finding of infection before administering a TNF-α inhibitor. The efficacy of prophylaxis is not 100%, however, so there were some patients who not only had complications of tuberculosis, but in whom symptoms rapidly exacerbated and resulted in death. Since there is a high possibility that death was due to an immune reconstitution inflammatory syndrome, it is necessary to consider re-administering biologics, or administer them continuously without interruption. As concerns non-tuberculous mycobacteriosis (NTM) which is rapidly increasing in Japan, on the other hand, its clinical manifestation is non-uniform and lacks effective therapeutic drugs, so administration of biologics had been considered to be contraindicated, but from a close analysis of clinical cases, there is a growing recognition that biologics can be administered under certain conditions.

Key words: Biologics, TNF-α, Acid-fast bacilli, Tuberculosis, Non-tuberculous mycobacteriosis

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Review Article

NONTUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE

Seigo KITADA

Abstract The prevalence of nontuberculous mycobacterial (NTM) pulmonary disease is increasing in Japan and worldwide, and the importance of proper diagnosis and management of the disease has been recently recognized. *Mycobacterium avium* complex (MAC) is the most common and important causative agent of pulmonary disease among nontuberculous mycobacteria. I have described the latest epidemiology of NTM lung disease, clinical feature, disease type, disease progression, diagnosis including serodiagnosis, and treatment strategy of MAC lung disease in this report. There are a lot of unsolved problems in the field of NTM lung disease, therefore, further investigations are required.

Key words: Epidemiology, *Mycobacterium avium* complex pulmonary disease, Clinical feature, Diagnosis, Serodiagnosis, Treatment

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EXPERIENCE OF USE OF NEW ANTI-TUBERCULOUS DRUG, DELAMANID IN MULTI- AND EXTENSIVELY DRUG RESISTANT TUBERCULOSIS CASES IN OUR HOSPITAL

Masao OKUMURA and Takashi YOSHIYAMA

Abstract [Objective] We experienced use of new anti-tuberculous drug, Delamanid in multi- and extensively drug resistant tuberculosis (M (X) DR-TB) in our hospital.

[Materials and Methods] Fifteen cases who were diagnosed M(X)DR-TB had been used Delamanid in our hospital from 2014 to 2015.

[Results] The gender distribution consisted of eleven males and four females in M(X)DR-TB. The mean age was 53.3 years old in male and 28.3 years old in female. Japanese were eight cases, and Chinese were five cases, and other countries patients were two cases. Twelve cases were MDR-TB cases, and three cases were XDR-TB cases. Six cases of fifteen cases were sputum culture positive before using Delamanid. Two cases (13.3%) had been appearanced QTc extension in EKG by using Delamanid. But these cases had not seen symptom. Other typical side effects had not seen. Six cases (40.0%) of fifteen cases had done surgical resection. One case of fifteen cases had been died with intractable pneumothorax, and one case had been discontinued for leukopenia. All cases containing two discontinued cases had obtained negative conversion of sputum culture.

[Conclusion] We experienced new anti-tuberculous drug, Delamanid. If we add Delamanid only for MDR-TB patients with only one or two sensitive anti-tuberculous drugs, it will be possible to make anew resistance. We used one more another new drug, for example Linezolid or high dose isoniazid or Meropenem and Ampicilin Clavulanate acid with Delamanid and sensitive anti-tuberculous drugs. We need to investigate risk and benefit when we use new anti-tuberculous drug. We need not to make more another MDR-TB cases.

Key words: Delamanid, MDR-TB, XDR-TB, Chemotherapy, Surgical resection

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Review Article

CONTROLLING TUBERCULOSIS IN FOREIGN-BORN PERSONS IN JAPAN

Eriko MORINO, Jin TAKASAKI, and Haruto SUGIYAMA

Abstract Controlling tuberculosis (TB) among foreign-born persons is an important issue in Japan. The number of foreign-born patients with TB has been slightly increasing yearly, whereas that of Japan-born patients with TB has been decreasing. Some foreign-born persons visited Japan with active TB due to the lack of useful medical checks performed before immigration. The percentage of those with TB among foreign-born persons is high (up to 43%) in the younger generation, especially those in their 20s. Currently, multidrug-resistant TB occurs at a low frequency in Japan; however, there is a danger of persons being easily immigrated into Japan from high-burden countries. Physicians need to be aware that TB is an imported infection. Additionally, a strategy for controlling TB in foreign-born persons (e.g., performing medical checkups before immigration, conducting target medical checkups of high-risk people for TB, administering chemoprophylaxis to foreigners, reconsidering the public medical insurance system for TB treatment, and offering patient support) needs discussed.

Key words: Tuberculosis, Foreign-born persons, Japan

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CLINICAL INVESTIGATION OF 6 CASES OF TUBERCULOUS SPONDYLITIS

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and [2]Katsuhiko AOYAMA

Abstract [Objective] A delay in the diagnosis of tuberculous spondylitis can result in worsening of the condition. We investigated previously reported cases of tuberculous spondylitis, as well as cases experienced in our hospital, to identify factors that are useful in the diagnosis.

[Materials and Methods] We retrospectively evaluated six cases of tuberculous spondylitis diagnosed in our hospital between October 2007 and September 2012, and an additional 23 cases that had been reported in Japan between 1994 and 2014.

[Results] The median age of our six patients was 78.5 years and five were women. In all cases, the focal lesion was seen in 2−3 adjacent vertebrae; four patients had miliary tuberculosis and five had lower back pain. All patients received oral treatment for 10−12 months. Among the 23 patients previously reported, 57% were women, and a focal lesion was found in 2−3 adjacent vertebrae in 86%. In addition, 57% had miliary tuberculosis and 65% had lower back pain. A personal and family history of tuberculosis was found in 20% and 26%.

[Discussion] Radiographic assessment and microbiological testing of areas other than the chest and spine are useful in the diagnosis of tuberculous spondylitis. Furthermore, lower back pain, lower extremity symptoms, and personal and family history of tuberculosis are important factors.

[Conclusion] When tuberculous spondylitis is suspected, diagnosis may be possible by investigating focal lesions in areas other than the spine.

Key words: Tuberculous spondylitis, Miliary tuberculosis, Extrapulmonary tuberculosis, Diagnosis, Clinical feature

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Original Article

EXTERNAL QUALITY ASSESSMENT OF ANTI-TUBERCULOSIS DRUG SUSCEPTIBILITY TESTING FOR DIAGNOSING EXTENSIVELY DRUG-RESISTANT *MYCOBACTERIUM TUBERCULOSIS*

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Abstract [Objective] The infectious disease control law has been amended in May 2015, and the category definition of *Mycobacterium tuberculosis* as infectious pathogen has been changed, following the definition of extensively drug-resistant *M.tuberculosis* (XDR-TB) by World Health Organization. To assess the diagnostic capacity of XDR-TB, we conducted an external quality assessment (EQA) for the anti-tuberculosis drug susceptibility testing (DST).

[Method] A total of 10 *M.tuberculosis* strains with known drug susceptibility were sent to each participating laboratory. The drugs assessed were isoniazid (INH), rifampicin (RFP), streptomycin (SM), ethambutol (EB), levofloxacin (LVFX), and kanamycin (KM). DST was performed using each routine method(s), and the results were compared with the judicial diagnoses. The sensitivity, specificity, overall agreement (efficiency) and kappa coefficient were calculated for each drug tested. In addition, the diagnostic accuracy of multidrug-resistant *M.tuberculosis* (MDR-TB) and XDR-TB was assessed.

[Results] A total of 88 institutes including 67 hospitals, 16 commercial laboratories, and 5 public health laboratories participated in the EQA. With 2 laboratories submitting 2 sets of results, a total of 90 independent data sets were analyzed. As for INH, RFP and LVFX, the efficiency was over 95%, but we found two strains each for SM, EB and KM with the efficiency less than 95%. Especially, strain 1 and strain 2 showed efficiency of 72.2% and 71.1% to SM, respectively. This error was mainly found in a certain test kit. If we consider the passing score as showing ≧ 95% sensitivity and specificity both to INH and RFP, the diagnostic accuracy of MDR-TB was 92.2% (83/90) in this study. With the same criteria to INH, RFP, LVFX and KM, that of XDR-TB was 79.7% (63/79).

[Discussion] The diagnostic capacity of XDR-TB was not sufficient in the current study. Good case management and pathogen control requires higher accuracy. The government may need to conduct a constant EQA and relevant remedial actions.

Key words: *Mycobacterium tuberculosis*, Drug susceptibility testing, External quality assessment, Extensively drug-resistant *Mycobacterium tuberculosis*

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