Original Article

EXPERIENCE OF RAPID ORAL DRUG DESENSITIZATION THERAPY IN THE TREATMENT OF MYCOBACTERIAL DISEASE
— 2. RIFAMPICIN —

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Abstract [Background] Hypersensitivity reactions to rifampicin (RFP) are the severe problem in tuberculosis (TB) treatment and *Mycobacterium avium* complex (MAC) disease treatment. RFP is the most effective for TB and one of the key drugs in MAC treatment. In Japan, desensitization therapy for anti-mycobacterial drugs is performed according to the propositions of Japanese Sociery for Tuberculosis (JST), but it needs 16 days. We investigated the rapid oral drug desensitization (RODD) that could be finished in a shorter period.

[Objective] To investigate the success rate of RODD for allergic reaction to RFP.

[Method] RODD for RFP was performed for 29 cases, who were interrupted in RFP treatment in the JATA Fukujuji Hospital between 2012 and 2016.

[Result] RFP RODD was administered to fourteen pulmonary tuberculosis (PTB) patients and fifteen MAC patients. The success rate of PTB patients was 85.7% and of MAC patients was 66.7%.

[Conclusion] RODD is one of the desensitization in RFP re-administration.

Key words: Tuberculosis, Pulmonary *Mycobacterium avium* complex disease, Rifampicin, Rapid oral drug desensitization

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Original Article

RETROSPECTIVE ANALYSIS OF TREATMENT OF LATENT TUBERCULOSIS INFECTION IN JAPAN

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Abstract [Background and objective] Japanese guidelines of treatment of latent tuberculosis infection (LTBI) recommends the use of isoniazid (INH) as the primary drug, and rifampicin (RFP) for contacts of INH resistance or persons with adverse drug reaction of INH, and also recommends the use of computed tomography (CT) scan for the detection of active tuberculosis when the candidate is with risk of active tuberculosis. However, the information of current status of treatment of LTBI in Japan is limited and need to be clarified.

[Method] Multicenter retrospective questionnaire survey of Ryoken group for the X-ray normal candidate of treatment of LTBI on the demographic information, reason of investigation of tuberculosis infection, method of diagnosis of tuberculosis infection, name of used drugs, adverse drug reaction (ADR), treatment result and occurrence of tuberculosis diseases during follow-up period.

[Results] Among 1570 persons, 1203 persons were examined as contacts, 115 persons with immunosuppression, 244 persons with immunosuppression therapy and 21 persons with Koch phenomenon. 519 persons were not examined with CT scan and 1044 persons were examined with CT scan. 653 persons were normal, 93 persons were with inactive tuberculosis or calcification, 28 persons were active tuberculosis, 268 persons were non-tuberculosis diseases and 2 persons were judged as primary tuberculosis. One case that was judged as active tuberculosis by CT findings later was treated with isoniazid for 6 months and there was no deterioration during the 9 months follow up period. The analysis of cases of seven hospitals that reported active tuberculosis cases detected by CT scan showed that the proportion of active tuberculosis among all persons with CT scan varied from 4% to 32%. 1494 persons were treated with INH, 43 persons were with RFP, one person was with INH and RFP, three contacts of multi drug resistant tuberculosis were with ethambutol (EB), and 29 persons were with three or four drugs. Among the 1494 persons that were treated with INH, 237 persons (16%) suffered from ADR with modification of medicine and 185 persons of these suffered from liver dysfunction. Among these 237 persons with ADR, 41 persons restarted INH, 82 persons changed to RFP and 112 persons stopped treatment of LTBI. The final outcome of treatment of the 1494 persons with INH, 1162 persons (78%) completed treatment with the original regimen, 75 persons (5%) completed treatment with revised regimen, 188 persons (13%) defaulted, 58 persons (4%) transferred out, 1 person became active tuberculosis during treatment of LTBI. Among the 43 persons with RFP due to the drug resistance of the index case, no persons suffered from ADR and 42 persons (98%) completed RFP treatment and one person (2%) transferred out. Among the 82 persons that started RFP due to ADR of INH, 71 persons (87%) completed RFP treatment, 10 persons (12%) stopped treatment and 1 person (1%) changed again to INH and completed treatment. The proportion of ADR among those that started treatment of LTBI with INH is higher than those that started with RFP ($p=0.009$) and the proportion of completion is lower ($p=0.007$). One that started INH and RFP and three that started EB completed regimen. Ten persons developed tuberculosis diseases during the follow up period among 1494 persons that started INH treatment and no one developed tuberculosis diseases among 43 persons with RFP, one person with INH and RFP and three persons with EB. Among these ten persons, four persons were culture negative, three persons developed tuberculosis diseases with INH susceptible bacilli, one person with immunosuppression therapy developed INH resistant bacilli, and two contacts of INH susceptible tuberculosis developed INH resistant tuberculosis diseases. The risk of development to tuberculosis diseases was significantly higher among the age group of 15 to 29 (5/190, 2.6%), in comparison to other age group (5/1351, 0.4%), among the contacts of sputum smear 3+ positive index case (5/336, 1.5%) in comparison to the contacts with less smear positivity (1/682, 0.1%). There was no difference of development to tuberculosis diseases by the grade of QuantiFERON positivity and number of spots of T-SPOT.*TB*. The proportion of development to tuberculosis diseases was higher among the persons without CT scan (6/519, 1.2%) than persons with CT scan (4/1016, 0.4%) without significance and among contacts without CT scan (6/468, 1.3%) than contacts with CT scan and without active TB at the time of treatment of LTBI investigation (1/700, 0.1%) with significance. There was no difference of the proportion of development to tuberculosis diseases between defaulters (1/253, 0.4%) and completes (8/1303, 0.6%).

[Discussion] RFP treatment showed less ADR and better treatment result than INH treatment. The risk of development of drug resistance was 2/6 (33%) among the culture confirmed persons and this proportion was bigger than the previous report and we need further to follow up this result. The proportion of development to tuberculosis diseases among contacts with CT scan was lower than contacts without CT scan. However, this difference (1.2%) is less than the proportion of persons that were judged as active diseases by the investigation at the time of screening for treatment of LTBI. This means that many of these persons can be self

cured or cured with INH or RFP treatment. However, this cure obtained also with the risk of acquiring resistance to the used drug. The benefit, risk and cost analysis is necessary for the further expansion of CT scan including the risk of exposure to X ray. The limitation of this study is that this study is the retrospective study and the criteria of doing CT scan is not clear. However, usually CT scan is taken for those with higher risk of development of tuberculosis diseases and the fact that among the contacts with CT scan showed significantly less proportion of development to tuberculosis diseases means that CT scan reduces the risk of development to tuberculosis diseases actually.

Key words: Latent tuberculosis infection, Computed tomography, Rifampicin

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Case Report

A RARE CASE OF *MYCOBACTERIUM AVIUM* INFECTION IN THE PULMONARY BULLA

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Abstract A 68-year-old woman complaining of right back pain was admitted to our hospital. Chest X-ray showed a bulla with a fluid level in the right upper lung field. Percutaneous tube drainage of the bulla was performed. *Mycobacterium avium* was isolated and identified from intrabullous fluid culture. The fluid in the bulla gradually increased, so the patient underwent an operation for partial resection of right upper lobe of the lung. Histopathological examination found mycobacteria, the intracystic fluid culture was positive for *M. avium*, thus yielding a diagnosis of *M.avium* infection in the bulla. Infected bulla caused by *M.avium* is very rare.

Key words: Nontuberculous mycobacteria, *Mycobacterium avium*, Infected bulla, Percutaneous tube drainage, Lung resection

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Case Report

SISTER CASE OF PULMONARY TUBERCULOSIS WITH AN INTRA-FAMILIAL TRANSMISSION ROUTE

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Abstract The spread of tuberculosis from elderly patients to younger family members has remained an important route of infection in Japan. We treated two sisters (18 and 20 years old) in whom tuberculosis developed in 2014. Tuberculosis had also previously developed in a grandmother and then in their father. When tuberculosis developed in their grandmother in 2004, the sisters received the treatment of latent tuberculosis infection (LTBI), however, they did not receive LTBI treatment again in their father in 2011, despite interferon-gamma release assays being positive. Though the grandmother died in 2013 due to the relapse of tuberculosis, the sisters did not treated again. The sisters developed active tuberculosis in 2014. We analysed the *Mycobacterium tuberculosis* strains obtained from the sisters and the grandmother with variable number of tandem repeats (VNTR), and found that the sisters and their grandmother had infected the same *M.tuberculosis* strain. This case may suggest that re-infection of *M.tuberculosis* occurred after LTBI treatment.

Key words: Interferon-gamma release assay (IGRA), Intra-familial transmission, Latent tuberculosis infection (LTBI), Secondary infection, Variable number of tandem repeats (VNTR)

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