

## Original Article

## A CLINICAL INVESTIGATION OF SEVEN PATIENTS WITH PULMONARY TUBERCULOSIS WHO DEVELOPED MIXED LIVER INJURY DURING ORAL ANTI-TUBERCULOSIS TREATMENT

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**Abstract** [Background] Liver injury is the most common and clinically significant adverse reaction to anti-tuberculosis drugs, sometimes resulting in a fatal outcome. It has been reported that liver injury induced by isoniazid and pyrazinamide, which has the potential to cause hepatocellular injury, has a risk of becoming severe; while an injury induced by rifampicin, which has the potential to cause cholestatic injury, rarely becomes severe. However, mixed liver injury has not been studied thoroughly.

[Methods] Of 321 tuberculosis patients who were admitted and treated in our hospital over the past 5 years, 7 patients (2.1%) who developed mixed liver injury due to the use of anti-tuberculosis drugs were clinically investigated through their medical records.

[Results] There were 4 male patients and 3 female patients, with a mean age of 66.7 (59–85) years. The mean duration from the start of oral anti-tuberculosis drugs to the onset of mixed liver injury was 28.5 days. In 2 of the patients, the event occurred within 2 weeks. Two of them had a total bili-

rubin level of  $>5$  mg/dl at the time of diagnosis. In 6 of the 7 patients, the liver injury improved on discontinuation of the anti-tuberculosis drugs. In the remaining 1 patient, the liver injury progressed even after discontinuation of the oral treatment, leading to death.

[Conclusion] Since mixed liver injury sometimes results in a fatal outcome, it is necessary to take adequate precautions.

**Key words:** Pulmonary tuberculosis, Anti-tuberculosis agents, Adverse reactions, Drug-induced liver injury, Mixed liver injury

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## USE OF REGULAR CHECK-UPS AFTER COMPLETION OF TREATMENT FOR LATENT TUBERCULOSIS INFECTION

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**Abstract** [Purpose] To evaluate the efficacy of regular examination (primarily by chest radiography) following treatment for latent tuberculosis infection (LTBI), we attempted to estimate the frequency and time to onset of active tuberculosis after completion of LTBI treatment.

[Objects & Methods] From the Japanese national surveillance data of 2008–2011, we extracted and analyzed the number of active tuberculosis cases after the end of LTBI treatment that was registered during 2008–09.

[Results] Among LTBI cases registered during 2008–09 ( $n=8951$ ), 56 active tuberculosis cases following LTBI treatment were detected by the end of 2011. Frequency of onset of active tuberculosis by the end of the second year after registration of LTBI cases were as follows: 0.57% (51/8951), all active tuberculosis cases; 0.10% (9/8951), smear-positive lung tuberculosis cases; and 0.22% (20/8951), all bacteria-positive lung tuberculosis cases. In 37 active tuberculosis cases for which the date of completion of LTBI treatment was available, 12 cases were diagnosed within 1 year and 22 within

2 years of the completion of LTBI treatment.

[Conclusion] The frequency of onset of active tuberculosis after completion of LTBI treatment was relatively low, but it did not decrease with time in the following 2 years. Hence, the validity of regular examination should be assessed, rather than specifying the duration of regular examinations after completion of LTBI treatment.

**Key words:** Tuberculosis, Latent tuberculosis infection, Follow-up examination, Chest radiograph, Surveillance

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## Original Article

## MEDICATION SUPPORT AND TREATMENT OUTCOME IN HOMELESS PATIENTS WITH TUBERCULOSIS

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**Abstract** [Purpose] We conducted a study on factors related to treatment outcome and medication support in homeless patients with tuberculosis.

[Methods] Participants were 433 homeless patients with tuberculosis newly registered in Osaka City between 2007 and 2009. We investigated factors related to treatment outcome (e.g., length of hospital stay, scheduled duration of outpatient treatment, and type of DOTS). Controls were 3,047 non-homeless patients with pulmonary tuberculosis newly registered in Osaka City during the same period.

[Results] Regarding medication support, 219 (70.4%) of the 311 patients with successful treatment received DOTS and completed the treatment during their hospital stay. Thirty-five (72.9%) of the forty-eight patients who did not complete treatment left the hospital at their own discretion, resulting in treatment failure/default. The rate of treatment failure/default in the homeless patients with pulmonary tuberculosis was 11.0%, significantly higher than that of non-homeless patients with pulmonary tuberculosis (6.5%;  $P < 0.001$ ). Among the 102 patients receiving community DOTS, medication compliance occurred at least 5 days a week in 66 patients (64.7%) and treatments failed or were interrupted in 10 patients (9.8%). The mean hospital stay was  $2.0 \pm 1.6$  months in patients with failed/defaulted treatment and  $4.4 \pm 2.5$  months in those with successful treatment. The scheduled duration of outpatient treatment was  $7.9 \pm 2.7$  months in patients with failed/defaulted

treatment and  $3.6 \pm 2.1$  months in those with successful treatment. Shorter length of hospital stay and longer scheduled duration of outpatient treatment were associated with a higher rate of treatment failure/default ( $P < 0.01$ ).

[Conclusion] Homeless patients with tuberculosis had a higher rate of treatment failure/default, most likely due to leaving the hospital at their own discretion. Patients with successful treatment generally completed treatment during their hospital stay. In contrast, patients who received community DOTS after discharge from the hospital had a higher rate of treatment failure/default, despite receiving medication at least 5 days a week. This suggests the need for adequate support, particularly in patients with a shorter hospital stay and those with a longer scheduled duration of outpatient treatment.

**Key words:** Tuberculosis, Homeless patient, DOTS, Treatment outcome, Duration of treatment, Self-discharge

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## EFFICACY OF THE TREATMENT FOR LATENT TUBERCULOSIS INFECTION AND DELAYED REACTIVATION OF TUBERCULOSIS

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**Abstract** [Purpose] To evaluate the efficacy of treatment for latent tuberculosis infection and delayed reactivation of tuberculosis.

[Method] During a large tuberculosis outbreak, 129 individuals who were in close contact with tuberculosis patients and subsequently tested strongly positive by the tuberculin skin test were followed up for 10 years after identification of the source case.

[Result] Of the 129 individuals, 105 received treatment for latent tuberculosis infection for 6 months as per recommendation, while the remaining 24 did not receive treatment, because most of them were above 30 years of age and were therefore discouraged from receiving treatment, as was done in the earlier times in Japan. Of the 105 individuals, 5 (4.8%) were newly diagnosed with tuberculosis, and the average duration from identification of the source case to reactivation of tuberculosis was 53 months. Of the 24 individuals who did not receive treatment for latent tuberculosis infection, 6 (25.0%)

were newly diagnosed with tuberculosis, and the average duration from identification of the source case to reactivation of tuberculosis was 8.2 months.

[Conclusion] The risk of active tuberculosis was reduced by 81.0% with treatment for latent tuberculosis infection, compared with that without treatment. Delayed reactivation of tuberculosis was observed among patients treated with isoniazid for latent tuberculosis infection for 6 months.

**Key words:** Tuberculosis, Outbreak, Latent tuberculosis infection, Efficacy of LTBI, Delayed reactivation of tuberculosis

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## Report and Information

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## — (4) Tuberculosis Treatment and Treatment Outcomes —

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**Abstract** The frequency of re-treatment among newly notified tuberculosis (TB) patients might be an indicator of inadequate prior treatment. In 2011, 22,681 patients were notified with TB, of which, 1,687 patients had received prior TB treatment (7.6% of those patients who presented with unknown treatment history were excluded). Nearly half of the re-treatment cases had received previous treatment after 2000 (n=766).

A standardized treatment regimen is the key to TB control. As for the initial treatment regimen, a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol (or streptomycin) is recommended; this regimen was initially used for the treatment of approximately  $\geq 85\%$  of all forms of TB in patients aged 15–54 years (patients with an unknown treatment regimen were excluded). Of the 11,556 patients who underwent TB treatment regimen with pyrazinamide and completed the course of treatment by the end of 2011, approximately 10% were unable to complete the 2-month-long regimen with pyrazinamide.

In 2011, 17,519 patients were newly notified with pulmonary TB (PTB). The proportion of patients who were hospitalized on the commencement of anti-TB treatment increased as the age increased above 30 years.

The median duration of hospitalization among newly notified TB patients in 2010 was 70 days for new sputum-smear positive PTB patients, 71 days for re-treatment sputum-smear positive PTB patients, 43 days for other bacteriologically positive PTB patients, 41.5 days for bacteriologically negative and other patients, and 46 days for extra-pulmonary TB patients. As of end-of-year 2011, the median treatment duration

for all forms of TB patients, newly notified in 2010, was 272 days.

The treatment success rates for new sputum-smear-positive PTB patients (n=8,242), re-treatment PTB patients (n=794), other bacteriologically positive PTB patients (n=6,358), and bacteriologically negative and other patients (n=2,883), registered in 2010 were 52.0%, 42.7%, 59.6%, and 60.4%, respectively.

The proportion of new sputum-smear-positive PTB patients, registered in 2009 and 2010, who died by the end of the following years were 26.9% and 27.8%, respectively.

The cause of death among TB patients, usually determined by physicians, has been collected through a TB surveillance system in Japan. The proportion of deaths caused by TB within one month of registration, among both the newly notified TB patients and the new sputum-smear-positive PTB patients, tended to be higher than that caused by other reasons (48.5% vs. 17.3% and 51.5% vs. 19.7%, respectively).

**Key words** : Tuberculosis, Treatment history, Treatment status, Duration of treatment, Treatment outcomes

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