Original Article

TIMING OF ANTIRETROVIRAL THERAPY INITIATION FOR HIV-INFECTED ADULTS WITH NEWLY DIAGNOSED TUBERCULOSIS

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Abstract [Background] There has been a discussion about the timing of antiretroviral therapy (ART) for HIV-positive adults with newly diagnosed tuberculosis (TB). Department of Health and Human Services guidelines in 2012 recommended early ART initiation. In 2016, the guideline was partly updated that treatment of tuberculosis should be started first, followed by ART within the first two weeks for patients with profound immunosuppression ($CD4^+$ T cell counts $<50\,\mu L$) and within eight weeks for others. In our practice, few patients could start ART as early as stated in the guideline. We, hereby, tested the hypothesis that it is difficult to evenly set the timing of ART initiation based only on the $CD4^+$ T cell counts.

[Methods] We conducted a retrospective study by using the past medical records of the HIV/TB co-infected patients who were admitted to our hospital from September 1995 to August 2015 and started ART for the first time after initiation of TB treatment. We examined characteristics of the patients, the timing of ART initiation, clinical courses, and mortality.

[Results] Fifty HIV/TB co-infected adults (median age 46 y.o., male: female=45:5) were included in this study. The number of patients who could start ART as recommendation was three out of 18 with $CD4^+$ T cell counts less than 50 cells/μL and three out of 32 with $CD4^+$ T cell counts not less than 50 cells/μL. The main reason for the delayed start of ART was adverse effects by anti-TB drugs, and the second was adverse effects by medications for the comorbid conditions or the preventive treatment. Seven patients developed immune reconstitution inflammatory syndrome (IRIS) after initiation of ART with deterioration of initial focuses of tuberculosis. Although most patients couldn't start ART on schedule as recommended, 90% of patients were able to start both TB and HIV therapy and survived. Whereas some patients got worse because of complications, no one died because of tuberculosis.

[Conclusion] As for treatment of HIV/TB patients, only a few cases could start early ART as the guidelines recommended. Early ART has also many risks under unstable clinical conditions. As mentioned in the hypothesis, it is difficult to set the timing of ART initiation evenly depending on the $CD4^+$ T cell counts. Delayed ART, after dealing properly with adverse effects of anti-TB drugs or complications, resulted in good prognosis.

Key words: HIV, Tuberculosis, Antiretroviral therapy, Immune reconstitution inflammatory syndrome

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Original Article

CLINICAL CHARACTERISTICS OF PATIENTS WITH *CLOSTRIDIUM DIFFICILE* INFECTION DURING TUBERCULOSIS TREATMENT, AND A PROPOSAL FOR USING TAPERED AND THEN MAINTAINED VANCOMYCIN THERAPY FOR RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION

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Abstract [Background/Objectives] *Clostridium difficile* infection (CDI) is steadily rising worldwide in incidence and the severity of CDI has increased in recent years. CDI is known to develop after antibiotic administration, but tuberculosis (TB) medication is not commonly associated with its development. We herein describe the characteristics of patients with CDI during TB treatment, and propose a method for administering vancomycin (VCM) therapy, which is tapered and then maintained, for recurrent CDI.

[Materials and Methods] We retrospectively evaluated 285 TB patients admitted to our hospital between January 2012 and December 2015. We analyzed the clinical characteristics of patients with CDI during TB treatment, and we conducted a comparison between CDI and non-CDI patients. Furthermore, we evaluated the effectiveness of VCM therapy, tapered and then maintained, for recurrent CDI. The regimen for administering VCM therapy, tapered and then maintained, was as follows: 125 mg four times a day for 1 week−10 days, 125 mg twice a day for 1 week, 125 mg daily for 1 week, 125 mg once every other day for 1 week, 125 mg every 3 days for 1 week, and finally 125 mg every 1 week until discharge or the completion of TB treatment.

[Results] A total of 285 TB patients were included in this study. CDI developed in 35 of these 285 TB patients (12.3%) with a CDI incidence of 18.02 cases per 10,000 patient-days. Many CDI patients had a previously identified risk profile with factors such as advanced age, undernutrition, and multiple comorbidities. Twenty of the 35 CDI patients had a recurrence (57.1%), and there were also multiple recurrences. CDI patients required long-term hospitalization and 10 of the 35 patients died (28.6%). Comparison between the 35 CDI patients and 250 non-CDI patients revealed significant differences in age, sex, albumin, lymphocytes, dementia, bedridden state, tube feeding, antibiotics use after hospitalization, length of hospitalization, and the death rate ($p < 0.05$). VCM therapy, tapered and then maintained, for recurrent CDI did not interrupt the treatment of TB, nor was there CDI recurrence after this maintenance therapy regimen.

[Conclusions] CDI tends to develop during TB treatment in patients with poor general conditions and advanced age. There is a high CDI recurrence rate in patients receiving TB treatment and deaths are common. VCM therapy, tapered and then maintained, for recurrent CDI suppresses CDI recurrence and is effective and useful for continuation of TB treatment.

Key words: Tuberculosis, *Clostridium difficile* infection, VCM therapy tapered and maintained

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Review Article

PATHOGENESIS AND PATHOPHYSIOLOGY OF CHRONIC PULMONARY ASPERGILLOSIS

Takayoshi TASHIRO

Abstract In Japan, chronic pulmonary aspergillosis is divided into simple pulmonary aspergilloma and chronic progressive pulmonary aspergillosis, which includes chronic necrotizing pulmonary aspergillosis (CNPA) and chronic cavitary pulmonary aspergillosis (CCPA). CNPA is defined as an indolent, cavitating process in the lungs due to invasion of lung tissue by *Aspergillus* spp. CCPA is defined as a chronic non-invasive pulmonary aspergillosis, which shows one or multiple cavities with or without an aspergilloma. Denning et al. described the two following radiological patterns in CCPA: one that initially manifests with ill-defined areas of consolidation that progresses to form well-defined cavities and another that has an overt progression of preexisting cavities observed radiologically. The radiological features of the former are the same as those of CNPA. In contrast, subacute invasive pulmonary aspergillosis, defined as invasive aspergillosis occurring over 1 to 3 months, is not as same as CNPA, which occurs over months or years. Chronic pulmonary aspergillosis includes several subtypes; therefore, we must understand their pathogenesis and pathophysiology and need to pay attention to the definition of the cases when reading the medical reports.

Key words: Chronic necrotizing pulmonary aspergillosis, Chronic cavitary pulmonary aspergillosis, Subacute invasive pulmonary aspergillosis, Chronic progressive pulmonary aspergillosis

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Review Article

PATHOLOGY OF TUBERCULOSIS

Yoshinori KAWABATA

Abstract Tuberculosis, particularly pulmonary tuberculosis, is a serious disease in humans. Although its pathology was mostly established by 1950, many subjects remain unsolved including the causes of various types of caseous necrosis (such as the primary focus, caseous pneumonia, necrosis in immunocompromised patients, necrosis following exudation, and necrosis following production), the cause of lytic changes of caseous necrosis, and the original portion, manner, and causes of reactivation. In this article, I emphasize the diversity of host-parasite relationships associated with the degree of cellular immunity, and also try to explain the reasons for the various reactions of the host.

Key words: Tuberculosis, Pathology, Pathogenesis, Reactivation, Immunohistochemistry