The Effect of Combined Therapy According to the Guidelines for the Treatment of Mycobacterium avium Complex Pulmonary Disease

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Abstract

Objective To investigate whether the combined therapy according to the guideline proposed by American Thoracic Society (ATS) and Japanese Society for Tuberculosis (JST) is clinically appropriate for Mycobacterium avium complex (MAC) pulmonary disease.

Patients Seventy-one patients in whom MAC pulmonary disease was diagnosed at Kawasaki Medical School and our associated ten hospitals were prospectively studied.

Results Seventy-one patients with Mycobacterium avium complex (MAC) pulmonary disease were 27 males and 44 females with a mean age of 64.4 ±10.2 years old. Patients received 400 mg/day or 600 mg/day of clarithromycin plus ethambutol, rifampicin, and initial streptomycin for 12 months. Among 71 patients who received more than 12 months of therapy, 41 patients (57.7%) converted their sputum to negative within six months after the initiation of this regimen, 16 of 41 patients (39.0%) relapsed, and 23 of 71 patients (32.4%) obtained clinical improvement on chest X-ray and/or clinical symptoms. The mortality rate had a comparatively good prognosis with a low incidence of 2.8%. Although the species of pathogen (M. avium or M. intracellulare) did not significantly affect the conversion rate or clinical improvement, the infectious form with or without respiratory underlying disease, the characteristics and extent of lesion on chest X-ray, and the dose of clarithromycin significantly influenced the conversion rate or clinical improvement. There were no problems concerning adverse reactions for this regimen.

Conclusion This combined therapy, according to the guideline proposed by ATS and JST, was one of the effective treatments compared to the clinical effect for pulmonary tuberculosis. The development of new companion drugs for MAC pulmonary diseases is needed.

Key words: combined chemotherapy, guideline of ATS and JST, MAC pulmonary disease, clinical effect

Introduction

Mycobacterium avium complex (MAC) pulmonary disease is the most common nontuberculous mycobacterial infection in Japan, and is increasing in incidence (1). Antituberculous regimens consisting of three or four drugs have been used empirically, but the rates of successful treatment are varied (sputum conversion rate from 25 to 80%) and there were frequent relapses (2–6). Wallace et al (7) and Dautzenberg et al (8) reported that clarithromycin (CAM) is clinically effective in the treatment of MAC pulmonary disease as a single agent, but the resistance for CAM develops in failed cases. To heighten the efficacy and prevent the development of CAM resistance, Wallace et al initiated clinical trials of regimens including CAM, ethambutol (EB), rifabutin (RBT) or rifampin (RPF), and initial streptomycin (SM), and reported that the regimen achieved satisfactory results (9). The American Thoracic Society (ATS) recommended a four-drug regimen including CAM, ethambutol (EB), rifabutin (RBT) or rifampin (RPF), and initial streptomycin (SM), and reported that the regimen achieved satisfactory results (9). The American Thoracic Society (ATS) recommended a four-drug regimen including CAM or AZM, RFP or RBT, EB, and initial aminoglycoside (SM or kanamycin) for MAC pulmonary disease in 1997 (10). Furthermore, the Japanese society for Tuberculosis (JST) also recommended a four-drug regimen including CAM, RFP, EB, and initial aminoglycoside in 1998 (11). However, reports that substantiate the clinical efficacy of the CAM-containing regimen for MAC pulmonary disease are few.

For that reason, we prospectively investigated whether or
Patients and Methods

Patients

Patients in whom MAC pulmonary disease was diagnosed at Kawasaki Medical School and our ten associated hospitals from April 1998 to March 2002 were selected. Clinical features were as follows: age, sex, underlying disease, microbiological findings, radiological findings, dose and duration of CAM, RFP, EB, SM, clinical efficacy and adverse reactions. The diagnostic criteria of nontuberculous mycobacterial infection proposed by ATS were satisfied.

Inclusion criteria for this study included positive sputum cultures for MAC at the time of entry into the study. Other inclusion criteria included availability for long-term follow-up over 12 months and aggravation of symptoms and/or chest radiograph findings. We included only the patients who had at least 12 months of drug therapy.

Protocol

A four-drug regimen that consisted of RFP 450 mg, EB 400 mg, CAM 600 mg (weight ≥ 50 kg) or 400 mg (weight <50 kg) if possible 800 mg (weight ≥ 50 kg) (CAM 600 mg had not been approved for clinical use by the Ministry of Health and Welfare in Japan) given daily by way of mouth, and streptomycin 1g intramuscularly given three times a week for the initial two to six months of therapy was used as a standard regimen. The overall treatment period was at least 12 months except for patients who had severe adverse side effects.

Patients were admitted to Kawasaki Medical School and our ten associated hospitals for the evaluation of baseline conditions and monitoring of compliance and adverse events at the initiation of the therapy. Routine expectorated sputum was submitted for examination on three consecutive days at entry into the study. The sputum was examined with Ziehl-Neelsen staining. Specimens submitted for culture were digested and decontaminated by the sodium hydroxide method, and the samples were inoculated onto slants of 3% Ogawa egg medium (Japan BCG, Tokyo, Japan). Mycobacteria were identified and differentiated by growth characteristics and conventional biochemical tests. Mycobacterium avium and Mycobacterium intracellulare were identified by the Amplicor polymerase reaction (PCR) assay. Patients were examined every two weeks for the first three months, every four weeks thereafter during the therapy, and at least every two months during the follow-up after completion of the therapy. Sputum was submitted for examination at every visit. Computed tomography (CT) was performed initially in all patients to evaluate the lesions including bronchiectasis and cavity, and underlying pulmonary conditions. A chest X-ray was taken initially and at least every two months thereafter. Disease extent was evaluated on the basis of both chest X-ray and chest CT findings. Peripheral blood cell count, aminotransferase, total bilirubin and serum creatinine tests were performed every visit during the therapy. Patients were advised to consult an otolaryngologist and an ophthalmologist initially, and as needed thereafter. Visual activity test, perimetry, and red-green color discrimination test were performed routinely to check for EB toxicity at least each month.

Clinical efficacy

Clinical efficacy was evaluated on the basis of sputum conversion rate, sputum relapse rate, clinical improvement containing radiological findings though the opinions of the attending respiratory specialists were included. Sputum conversion was defined as three consecutive negative sputum cultures within six months, with the time of conversion defined as the date of the first negative culture. If the patient could not expectorate sputum, it was considered that sputum had converted to negative. Sputum relapse rate was defined as two consecutive positive cultures after sputum conversion. Clinical improvement was defined as “improving” a decrease of abnormal shadows on chest X-ray and improvement of clinical symptoms, “unchanging” nearly the same radiological findings and clinical symptoms, and “worsening” an increase of abnormal shadows and worsening of clinical symptoms.

Statistical analysis

All results are presented as mean±SD. A comparison of characteristics of the patients was done by the unpaired Student’s t test. A value of p<0.05 was considered statistically significant. Multivariate analysis was not performed because of the small sample size.

Results

Background

From April 1998 to March 2002, 102 patients were newly given a diagnosis of MAC pulmonary disease at eleven hospitals. Among 102 patients, 31 patients were ineligible and the primary reasons for ineligibility were as follows: difficult to visit regularly (geographic distance etc.) in 21, noncompliance in seven, minimal symptoms and no signs of aggravation during the previous six months in three patients. The other 71 patients (69.6%) fulfilled the eligibility criteria and were enrolled in the protocol. The background of the eligible 71 patients is listed in Table 1. All patients were Japanese with a mean age of 64.4±10.2 years old (44 to 80 years old). The ratio of male and female was 27 : 44. All patients came from their own home. Five patients had been previously bedridden. Twenty-one patients were current smokers, 18 were ex-smokers, and 11 drank alcohol regularly. Forty-eight pa-
Table 1. Background of 71 Patients with MAC Pulmonary Disease

| Age years | 44–80 (64.4±10.2) |
| Gender, M/F | 27/44 |
| Previous physical activity |  |
| Bedridden | 5 (7%) |
| Smoking habit |  |
| Current smoker | 21 |
| Ex-smoker | 18 |
| Chronic alcoholism | 11 (15%) |
| Underlying disease |  |
| Respiratory disease | 33 (46%) |
| Old pulmonary tuberculosis | 22 |
| Bronchiectasis | 5 |
| Pneumococcosis | 3 |
| Pulmonary emphysema | 2 |
| Pulmonary fibrosis | 1 |
| Non-respiratory disease | 15 (21%) |
| Gastrointestinal disease | 8 |
| Endocrine disease | 3 |
| Collagen disease | 2 |
| Psychological disease | 1 |
| Hematological disease | 1 |
| Corticosteroid administration | 2 (3%) |
| Previously healthy | 23 (33%) |
| Prior antituberculous drug administration | 20 (28%) |

*Data expressed as mean±S.D.

Table 1. Background of 71 Patients with MAC Pulmonary Disease

For the patients with MAC pulmonary disease, 71 patients were begun on the regimen of this protocol according to ATS guideline. The dose of CAM was 400 mg/day in 34 patients, 600 mg/day in 35, and 800 mg/day into two groups separated by weight according to below or above 50 kg. Among 71 patients, 17 patients (23.9%) needed modification of companion drugs during the therapy because of adverse reactions. The choice of companion drugs was left to the attendant doctor’s discretion.

**Radiological and laboratory findings**

Of the 71 patients who received more than 12 months of therapy, the distribution of lesions consisted of bilateral lesions in 55 patients, right in 10, and left in six. Forty patients (56.3%) had small nodules and/or bronchiectasis and 39 (54.9%) and cavitory lesions. Regarding the extent of the lesion, minimal disease within one-third of unilateral lung field was found in 26 patients (36.6%), moderately advanced disease within the unilateral lung field in 37 (52.1%), and far advanced disease throughout the unilateral lung field in eight (11.3%).

Among the strains isolated from the 71 patients, 37 strains were *Mycobacterium avium*, and 34 strains were *Mycobacterium intracellulare*.

**Clinical efficacy**

**Sputum conversion rate** (Figure 1)

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**Clinical efficacy**

**Sputum conversion rate** (Figure 1)

Sputum conversion rates separated into the dose of CAM (400 mg/day, 600 mg/day, and 800 mg/day) was the most
significantly improved in patient’s group of 600 mg/day (71.4%). However, there were no significant differences concerning the patient’s age, weight, and nutritional condition such as albumin at the initiation of treatment and severity such as extent of lesion between the group administered CAM 400 mg/day and the group administered CAM 600 mg/day. Separating into two kinds of strains between M. avium (57.6%) and M. intracellulare (56.7%), there was no significant difference in either group. However, regarding the existence of respiratory underlying disease or the extension of lesion, the sputum conversion rates were significantly poorer in patients with respiratory diseases, such as healed pulmonary tuberculosis, as the underlying disease and in those with advanced disease throughout the unilateral lung field.

Sputum relapse rate (Figure 2)

Sputum relapse rates, as separated into the dose of CAM were not significantly different among the three groups. When separated into the two strains of M. avium and M. intracellulare, and regarding the existence of respiratory disease or the extent of lesion, there was no significant difference in the sputum relapse rates.

Clinical improvement (Figure 3, Table 2)
The overall outcome of this regimen was as follows: improved in 23 patients (32.4%), unchanged in 27 (38.0%), worsened in 19 (26.8%) and death in two (2.8%). The clinical improvement, as separated into the dose of CAM was also better in patient’s group of 600 mg/day (37.1%) than in patient’s group of 400 mg/day (26.5%). When separated into the two strains between M. avium (33.3%) and M. intracellulare (30.0%), there was no significant difference between these both groups. However, regarding the existence of respiratory underlying disease or the extent of lesion, clinical improvement was the worst in patients with respiratory underlying disease and advanced disease throughout the unilateral lung field.
**Adverse reaction**

Adverse reactions, as separated into the dose of CAM, are shown in Table 3. For CAM of 400 mg/day, adverse reactions appeared in 7 of 34 patients (20.6%) (vertigo in three, liver dysfunction in two, fever in one, and eruption in one), while with CAM of 600 mg/day, adverse reactions appeared in 9 of 35 patients (25.7%) (liver dysfunction in three, visual disturbance in two, gastrointestinal symptoms in two, vertigo in one, and eruption plus gastrointestinal symptoms in one). With CAM of 800 mg/day, adverse reactions appeared in one of two patients. However, there were no significant differences among three groups regarding the appearance rate of adverse reactions. The overall appearance rate of adverse reactions was 23.9%.

**Current status**

Of the 71 patients who were registered in this study, 54 patients were receiving the regimen of RFP+EB+SM+CAM according to the guideline of ATS for at least 12 months. The mean duration of administration of this regimen was 13.4±5.6 months (1-28 months) and the mean duration of follow-up was 16.8±6.9 months (12-36 months).

The overall mortality rate was comparatively good in 2.8% (only two patients). The causes of death were advanced MAC pulmonary disease in one patient and complicating bacterial pneumonia in one. Two of the patients who died were elderly and had a past history of healed pulmonary tuberculosis.

The clinical course of 25 patients who had clinical improvement of unchanging or worsening could be followed-up for six months after the completion of the treatment was as follows: non-therapy in 12 patients, new quinolone (levofloxacin) administration in eight, surgical operation in five.

**Discussion**

The ATS recommended a four-drug regimen including CAM or AZM, RFP or RBT, EB, and initial aminoglycoside (SM or KM) for MAC pulmonary disease in 1997 (10). Subsequently, the JST also recommended a four-drug regimen including CAM, RFP, EB, and initial aminoglycoside in 1998 (11). However, prospective studies that substantiate the clinical efficacy of the regimen according to both guidelines are few. First, Wallace et al reported the efficacy of CAM containing the regimens for MAC pulmonary disease without AIDS (9). They reported intolerance of the high dose of CAM (2,000 mg/day) among elderly patients in their earlier study (13) and used 1,000 mg/day (from 15 to 20 mg/kg/day) of CAM (7, 9). Subsequently, the sputum conversion rate was significantly higher than that in our study (92% compared with 58%). This difference may be a result of three major factors. The first is that we included patients whose isolates were resistant to CAM, the second is a lower dose of CAM (400 mg/day, n=34), and the third is the severity of MAC pulmonary diseases of registered patients at the initiation of treatment.

It is unclear whether CAM should be withdrawn in cases with resistant strains. The possibility of synergistic effects of multiple drug regimens on resistant strains has not been disproven. Moreover, there is a possibility of polyclonal MAC infections with mixtures of susceptible and resistant strains, especially in pulmonary disease with nodules and bronchiectasis (15). Therefore, we did not mention the susceptibility tests for CAM or other antituberculous drugs. Though there were no significant differences concerning the patient’s backgrounds such as their age, weight, nutritional condition and severity of MAC pulmonary disease between the group of CAM 400 mg/day and the group of CAM 600 mg/day, we recognized that 600 mg/day of CAM was significantly more effective than 400 mg/day with other companion drugs in our study. However, at present CAM 600 mg/day has not been approved for clinical use by the Ministry of Health and Welfare in Japan. From now on, we should explain the increase of CAM dose as the basis of our data.

Recently, azithromycin (AZM) was appeared as a new macrolide antibiotic resembling CAM, and ATS has discussed the efficacy of AZM instead of CAM for the treatment of MAC pulmonary disease (10). But Ward et al reported that CAM showed a significantly higher sputum conversion rate (86%) than AZM (38%) (16). Therefore, a more effective antibiotic for MAC pulmonary disease than CAM has not yet been developed.

The most difficult problems when to start therapy, as the ATS recommendation also pointed out (10). In previous reports (14), the conversion rate was significantly higher in smear-negative, newly diagnosed and restricted lesion cases. In the long prospect, however, there is no guarantee that relapse will never occur after completion of the initial treatment, due to underlying diseases, including preexisting lung disorders and unknown factors common to elderly patients (17). Subsequently, it is also difficult to discontinue the therapy, although ATS recommend to continue the therapy for at least one year. In our study, the sputum relapse rate was high (39%) even if the therapy according to both guidelines was performed. Considering the results in the study by Tanaka et al (14) in which the CAM-containing four-drug regimen was continued for at least two years for MAC pulmonary disease, it is still not definite when to start and stop therapy.

Because the method of assessment was restricted to the sputum conversion rate of MAC strains before and after the treatment in the previous reports, we think it is difficult to evaluate the whole clinical effect of patients treated by the assessment. Therefore, we performed the assessment of clinical improvement considering the clinical symptoms and/or
the extent of lesion on chest X-ray or chest CT scan rather than including the subjective assessment. Subsequently, the clinical effectiveness (32.4%) was significantly poorer than the sputum conversion rate (57.7%). Namely, there was not always a relationship between the clinical effectiveness and sputum conversion rate. However, we found that the clinical improvement was better in patients without other underlying respiratory diseases, with narrowing extent of the lesion and without cavitory lesion. Regarding the species of pathogen (*M. avium* or *M. intracellulare*), there was no significant difference in the sputum conversion rate and clinical improvement.

Lastly, regarding the adverse reactions, gastrointestinal symptoms due to CAM, neurological symptoms due to EB or bone marrow suppression due to interaction with other combined drugs were mentioned in the combined therapy containing CAM (18). However, there were no significant differences among the three groups of 400 mg/day, 600 mg/day and 800 mg/day CAM regarding the appearance rate of adverse reactions. Because the overall appearance rate of adverse reactions (24%) was almost the same as that of other reports (14, 19), there were no problems concerning the safety of the CAM-containing four-drug regimen according to both guidelines.

In conclusion, the CAM-containing four-drug regimen according to the guideline proposed by either ATS or JST was comparatively efficacious for the initial treatment of MAC pulmonary disease. Otherwise, although there were no problems concerning adverse reactions, the clinical improvement was unsatisfactory considering the sputum conversion rate was low in patients who had prior therapy and those who were infected with CAM-resistant strains. The development of new companion drugs for MAC pulmonary disease that are as active as CAM and that can be tolerated by elderly patients is needed to further increase the sputum conversion rate and to avoid the induction of macrolide resistance.

References