GUIDELINES FOR CHEMOTHERAPY OF PULMONARY NONTUBERCULOUS MYCOBACTERIAL DISEASE —2012 Revised Version

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The Nontuberculous Mycobacteriosis Control Committee
of the Japanese Society for Tuberculosis
The Scientific Assembly for Infection and Tuberculosis
of the Japanese Respiratory Society

1. Background to these revised guidelines

In 2008, the Nontuberculous Mycobacteriosis Control Committee of the Japanese Society for Tuberculosis and the Scientific Assembly for Infection and Tuberculosis of the Japanese Respiratory Society (hereinafter, the Joint Guidelines Committee) published the 'Guidelines for chemotherapy of pulmonary nontuberculous mycobacterial disease—2008 interim guidelines'[1]. In the background, rifabutin (RBT) and clarithromycin (CAM) were approved for Japanese medical insurance coverage in August of that year for the treatment of pulmonary nontuberculous mycobacterial diseases. Headed by the American Thoracic Society (ATS) official guidelines[2,3], since the 1990s the worldwide standard chemotherapy for pulmonary *Mycobacterium avium* complex (MAC) disease has been based on oral triple therapy with CAM, rifampicin (RFP) or RBT, and ethambutol (EB), with the addition of intramuscular injections of an aminoglycoside for the first 2 to 3 months in severe cases. However, in Japan there were no pharmacological agents with official approval for the treatment of pulmonary nontuberculous mycobacterial diseases until 2008, so the Societies were unable to publish any therapeutic regimens as official guidelines. Accordingly, the 2008 interim guidelines represented a revolutionary change in the clinical management of pulmonary nontuberculous mycobacterial diseases in Japan.

However, at the time the 2008 interim guidelines were published neither RFP nor EB were officially approved for Japanese medical insurance coverage for the treatment of pulmonary nontuberculous mycobacterial diseases, and circumstances dictated that dosages had to be expressed ambiguously. Following the efforts of various concerned parties, RFP and EB gained official approval in May 2011, leading to these updated guidelines revising the 2008 interim guidelines. In these guidelines, in addition to pulmonary MAC disease we will recommend a chemotherapy regimen for *M.kansasii* disease. Pulmonary *M.kansasii* disease is the most responsive to chemotherapy of all pulmonary nontuberculous mycobacterial diseases, and the therapeutic regimens are relatively well established[2,3]. On the other hand, we will not refer in these guidelines to treatments for other pulmonary nontuberculous mycobacterial diseases for which evidence is lacking. Until further evidence becomes available, and we are able to publish updated guidelines, please refer to sources such as the official ATS 2007 guidelines[3] in treating mycobacterial infections not covered in these guidelines.

As we explained in the 2008 interim guidelines, the chemotherapy regimens set out below are not based on direct clinical evidence. They have instead been adapted to pulmonary nontuberculous mycobacterial disease, based on the results of several randomised comparative trials conducted with patients with disseminated MAC systemic disease, frequently seen in patients with end stage HIV infections before the introduction of highly active anti-retroviral therapy[4~6]. We need to accumulate clinical evidence through clinical trials of the efficacy of the chemotherapy regimens set out in these guidelines.

2. Standard chemotherapy regimens for pulmonary MAC disease

(1) Agents, dosages and methods of administration

Chemotherapy regimens for pulmonary MAC disease are based on triple therapy with RFP, EB and CAM. If necessary, streptomycin (SM) or kanamycin (KM) may be added.

Monotherapy for MAC infections is strictly contraindicated, as efficacy is poor, and in particular CAM resistant strains have been detected within a few months of CAM monotherapy[3]. The Joint Guidelines Committee recommendations for the standard dosages and methods of administration for adult Japanese patients are given in Table 1.

(2) Adverse reactions

For the details of common adverse reactions to the chemotherapy regimen set out in Table 1, please refer to the product information for the individual agents. The Manual for Management of Serious Drug Reactions produced by the Ministry of Health, Labour and Welfare (MHLW) Pharmaceutical and Food Safety Bureau is available from the Ministry homepage, and we recommend in particular the skin, liver, haematological, sensory (eyes), and sensory (ears) sections[7]. The most frequent

Table 1 Chemotherapy for pulmonary MAC disease, dosages and methods of administration

RFP	10 mg/kg (maximum 600 mg)/day once daily
EB	15 mg/kg (maximum 750 mg)/day once daily
CAM	600−800 mg/day (15−20 mg/kg) once or twice daily (800 mg to be divided doses)
SM or KM	each ≦15 mg/kg (maximum 1000 mg) intramuscular injection 2 or 3 times weekly

RFP: rifampicin; EB: ethambutol; CAM: clarithromycin; SM: streptomycin; KM: kanamycin

adverse reactions reported with the above combination therapy are taste dyscrasias and gastrointestinal disturbances. These are particularly common in elderly patients, so it is best to avoid commencing all three agents at the same time, for example adding one at a time at weekly intervals. Leukopenia and thrombocytopenia can occur within several months of commencing treatment. In most cases, the white cell count remains above 2,000/mm^3, and the platelet count above 100,000/mm^3. If counts fall below these levels, however, discontinuation of RFP should be considered. Widespread skin rashes can also occur. These are often caused by EB or RFP, and with desensitization therapy are usually manageable. Desensitization to RFP should be performed with reference to the recommendations by the Treatment Committee of the Japanese Society for Tuberculosis[8]. Treatment durations for EB exceed those for tuberculosis, so patients should be carefully monitored for vision impairment. Adverse reactions to RFP, EB, SM and KM should be managed appropriately with reference to the Japanese Society for Tuberculosis 'Guidelines for the Treatment of Tuberculosis'[9] and other sources. Blood tests should be performed frequently, particularly in the early phase of treatment, due to the risk of serious hepatic and haematological toxicity.

RBT is considered to have a somewhat stronger antimicrobial activity against MAC than RFP, and should be considered if RFP is ineffective or cannot be used. In general, RBT 300 mg is thought to be as effective as RFP 600 mg[10]. Uveitis is an adverse reaction specific to RBT. The symptoms of uveitis include injection and pain in the eyes, floaters, blurred or distorted vision, decreased visual acuity, and loss of central vision. These can usually be distinguished from EB-associated optic neuropathy (vision impairment, visual field narrowing, visual field defects, and disturbances of colour vision). In most reports, uveitis occurs within 2 to 5 months of commencing RBT. The mechanism of RBT-induced uveitis is thought to be toxic rather than allergic in nature, and the risk of uveitis correlates with the dosage per kilogram body weight[11]. If it does occur, uveitis should respond to discontinuation of RBT and corticosteroid eye drops. Recommencement of RBT is usually possible in most mild cases, but it must be ceased if symptoms or signs of uveitis recur. Plasma levels of RBT are known to increase by more than 50% when it is coadministered with CAM[12], thereby increasing the incidence of RBT-induced uveitis[13]. In a 2000 U.S. study, uveitis was seen in 1.8% of 391 patients on RBT 450 mg monotherapy, and in 8.5% of 389 patients on RBT 450 mg＋CAM 1000 mg combination therapy[14]. Accordingly, the initial dosage of RBT in combination with CAM is 150 mg/day, which may be increased to 300 mg/day after 6 months if no adverse reactions occur. Further caution regarding visual disturbances is required when EB is added to these 2 agents. In addition, the incidence of other adverse reactions, such as neutropenia, increases when CAM is coadministered with other agents.

(3) Consideration regarding commencement of treatment

Previously, there was a tacit understanding that treatment should commence as soon as a patient met the diagnostic criteria, but both Japanese and American authorities have expressed the viewpoint that treatment need not necessarily commence as soon as the diagnostic criteria are met. The timing of treatment commencement should be decided on an individual. In general, early diagnosis and early treatment are considered desirable, but with regard to adverse reactions in particular, there is a lack of evidence as to when it is appropriate to commence chemotherapy. The overall decision is presently left to the treating clinician. We recommend consultation with a specialist in this area regarding the treatment plan, including the above problems and indications for surgical intervention.

(4) Two types of pulmonary MAC disease

Pulmonary MAC disease is classified into two types according to the radiological findings[3]. The first is the cavitary (Cav) type, with multiple cavities mainly in the apices and upper lung fields. The second is the nodular bronchiectatic (NB) type, with bronchiectasis and multiple nodules mainly in the middle and lingular lobes. The Cav type is common in smoking males, and the NB type in non-smoking women aged over 50 years. Presently, over 90% of cases of pulmonary MAC disease diagnosed in Japan are of the NB type. Outcomes are often worse with the Cav than with the NB type[2)3)15], so the optimum chemotherapy should be commenced without delay, and surgical intervention should also be strongly considered for the Cav type. On the other hand, progression and outcomes are characteristically not uniform, but rather vary widely in the NB type.

(5) Drug sensitivity testing

With the exception of CAM, drug sensitivity testing, from which the therapeutic efficacy of agents used in the treatment of pulmonary MAC diseases, has not been established[3]. This is because CAM is the only agent effective as monotherapy against all pulmonary MAC diseases. For the other agents, we can anticipate efficacy as part of combination therapy, but little clinical efficacy has been demonstrated when they are used as monotherapy, so it is difficult to establish any form of drug sensitivity testing. CAM resistance is almost nonexistent at treatment commencement, so sensitivity testing is only performed in patients undergoing retreatment, or whose condition

is deteriorating following chemotherapy. Testing is performed in accordance with the ATS Guidelines[3], seeking the minimum inhibitory concentration (MIC) in a liquid medium. An MIC ≦4 μg/mL indicates sensitivity, and ≧32 μg/mL indicates resistance; MICs of 8 or 16 μg/mL are considered indeterminate. If CAM resistance is detected, it should be ceased. For indeterminate results, CAM is continued, and sensitivity testing repeated at regular intervals. CAM resistance is common with CAM monotherapy and with CAM＋fluoroquinolone (FQ) combination therapy[16], and both should be strictly avoided. It goes without saying that CAM resistant cases are difficult to treat, and there are no regimens that we can recommend. Empirically, we use combinations including RFP, EB, SM or KM, and various FQs. Further studies are required to determine the clinical efficacy of FQs in general, and the individual FQs in particular.

(6) Considerations regarding the duration of treatment

There is no evidence to support the duration of treatment recommended in the Japanese and U.S. guidelines, "Treat until cultures have been negative on therapy for 1 year"[1)~3)]. Accordingly, there is no basis on which to recommend that treatment can be stopped at that stage. The British Thoracic Society Guidelines recommend 2 years of chemotherapy[17], whereas a long term Japanese study reported better outcomes when treatment was continued beyond the period recommended in the ATS guidelines[18]. Further studies are required to determine the optimum duration of treatment.

3. Standard chemotherapy for pulmonary *M. kansasii* disease

Pulmonary *M.kansasii* disease is the most responsive to chemotherapy of all pulmonary nontuberculous mycobacterial diseases. RFP, EB, isoniazid (INH), aminoglycosides such as SM, CAM, FQs such as levofloxacin, and co-trimoxazole (ST) are all effective[3]. However, pyrazinamide and para-aminosalicylic acid (PAS) are ineffective. INH and SM resistance is frequently detected on *M.tuberculosis* sensitivity testing, but if the organism is RFP-sensitive adequate clinical response can be expected with combination therapy[3]. *M.kansasii* infections are often treated as tuberculosis initially, and a cure can be expected in almost all cases if combination therapy with INH, RFP and EB is continued until cultures have been negative on therapy for 1 year. The Joint Guidelines Committee recommendations for the standard dosages and methods of administration for adult Japanese patients are given in Table 2.

The proportion of RFP-resistant pulmonary *M.kansasii* infections in Japanese patients is low at less than 1％, and is almost never seen during initial treatment[19]. It is therefore unnecessary to perform sensitivity testing for all patients, and *M.tuberculosis* sensitivity testing should only be performed in patients undergoing retreatment, or when the therapeutic response to the standard treatment has been poor. As mentioned above, only the RFP sensitivity results need to be considered, and if RFP-resistance is detected, combination therapy including EB, SM, CAM, FQs or ST should be continued until cultures have been negative on therapy for 1 year. In cases of RFP-resistance, it is desirable to select the agents to be used on the basis of MICs for each agent, e.g. using liquid media, in consultation with a specialist facility.

Table 2 Chemotherapy for pulmonary *M.kansasii* disease, dosages and methods of administration

INH	5 mg/kg (maximum 300 mg)/day once daily
RFP	10 mg/kg (maximum 600 mg)/day once daily
EB	15 mg/kg (maximum 750 mg)/day once daily

Treatment durations are longer than for tuberculosis, so even at these dosages careful attention is required in case of visual disturbances.

INH: isoniazid; RFP: rifampicin; EB: ethambutol

Adverse reactions to RFP or EB should be managed with reference to the above section regarding adverse reactions during treatment of pulmonary MAC diseases. The main adverse reactions to INH are hepatic dysfunction, neuropathies, rashes and hypersensitivity reactions. Vitamin B_6 should be administered from the outset to prevent neuropathies in elderly patients, and patients with diabetes, alcohol dependency, or nutritional disorders. Adverse reactions should be managed appropriately with reference to the INH product information, the above-mentioned MHLW homepage[7], and the 'Guidelines for the Treatment of Tuberculosis'[9].

References

1) Nontuberculous Mycobacteriosis Control Committee of the Japanese Society for Tuberculosis, Scientific Assembly for Infection and Tuberculosis of the Japanese Respiratory Society: Guidelines for chemotherapy of pulmonary nontuberculous mycobacterial disease—2008 interim guidelines. Kekkaku. 2008 ; 83 : 731−733.

2) American Thoracic Society: Diagnosis and treatment of disease caused by non-tuberculous mycobacteria. Am J Respir Crit Care Med. 1997 ; 156 : S1−S25.

3) Griffith DE, Aksamit T, Brown-Elliott BA, et al; on behalf of the ATS Mycobacterial Diseases Subcommittee: An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007 ; 175 : 367−416.

4) Dautzenberg B, Truffot C, Legris S, et al.: Activity of clarithromycin against *Mycobacterium avium* infection in patients with the acquired immune deficiency syndrome. Am Rev Respir Dis. 1991 ; 144 : 564−569.

5) Chaisson RE, Benson CA, Dubé MP, et al.: Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. Ann Intern Med. 1994 ; 121 : 905−911.

6) Dubé MP, Sattler FR, Torriani FJ, et al.: A randomized evaluation of ethambutol for prevention of relapse and drug

resistance during treatment of *Mycobacterium avium* complex bacteremia with clarithromycin-based combination therapy. California Collaborative Treatment Group. J Infect Dis. 1997 ; 176 : 1225−1232.

7） Ministry of Health, Labour and Welfare Pharmaceutical and Food Safety Bureau: The Manual for Management of Serious Drug Reactions (http://www.mhlw.go.jp/topics/2006/11/tp1122-1.html)

8） Treatment Committee of the Japanese Society for Tuberculosis: Guidelines for desensitization therapy to anti-tuberculous drugs. Kekkaku. 1997 ; 72 : 697−700. (http://www.kekkaku.gr.jp/ga/ga-1.htm)

9） Japanese Society for Tuberculosis ed.: Guidelines for the Treatment of Tuberculosis. Nankodo, Tokyo, 2009.

10） McGregor MM, Olliaro P, Wolmarans L, et al.: Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. Am J Respir Crit Care Med. 1996 ; 154 : 1462−1467.

11） Shafran SD, Singer J, Zarowny DP, et al.: Determination of rifabutin-associated uveitis in patients treated with rifabutin clarithromycin and ethambutol for *Mycobacterium avium* complex bacteremia: a multivariate analysis. Canadian HIV Trial Network Protocol 010 Study Group. J Infect Dis. 1998 ; 177 : 252−255.

12） Hafner R, Bethel J, Power M, et al.: Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. Antimicrob Agents Chemother. 1998 ; 42 : 631−639.

13） Kelleher P, Helbert M, Sweeney J, et al.: Uveitis associated with rifabutin and macrolide therapy for *Mycobacterium avium intracellulare* infection in AIDS patients. Genitourin Med. 1996 ; 72 : 419−421.

14） Benson CA, Williams PL, Cohn DL, et al.: Clarithromycin or rifabutin alone or in combination for primary prophylaxis of *Mycobacterium avium* complex disease in patients with AIDS: A randomized, double-blind, placebo-controlled trial. The AIDS Clinical Trials Group 196/Terry Beirn Community Programs for Clinical Research on AIDS 009 Protocol Team. J Infect Dis. 2000 ; 181 : 1289−1297.

15） Harada S, Harada Y, Ochiai S, et al.: A clinical study of deceased cases of pulmonary *M.avium* complex (MAC) disease. Kekkaku. 2002 ; 77 : 709−716.

16） Griffith DE, Brown-Elliott BA, Langsjoen B, et al.: Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med. 2006 ; 174 : 928−934.

17） Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society: Management of opportunistic mycobacterial infections: Joint Tuberculosis Committee Guidelines 1999. Thorax. 2000 ; 55 : 210−218.

18） Kobashi Y, Matsushima T: The microbiological and clinical effects of combined therapy according to guidelines on the treatment of pulmonary *Mycobacterium avium* complex disease in Japan-including a follow-up study. Respiration. 2007 ; 74 : 394−400.

19） Suzuki K, Yoshida S, Tsuyuguchi K, et al.: Chemotherapy for pulmonary *M.kansasii* disease. The 80th annual meeting symposium "Treatment of non-tuberculous pulmonary mycobacteriosis." Kekkaku. 2006 ; 81 : 41−43.

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