

Multicentre, open label, randomised controlled trial comparing intermittent versus daily treatment for non-cavitary nodular/bronchiectatic *Mycobacterium avium* complex lung disease with rifampicin, ethambutol and clarithromycin (iREC): study protocol

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ABSTRACT

Introduction Standard treatment for nodular/bronchiectatic *Mycobacterium avium* complex lung disease (NB MAC-LD), excluding severe-status cases, differs between Japan and other countries. Internationally, three-drug combination intermittent treatment (three times a week administration) with macrolide, ethambutol and rifampicin is recommended, but a daily treatment regimen is recommended in Japan. To date, no randomised controlled study directly comparing intermittent treatment with daily treatment has been performed. The purpose of this study is to investigate the usefulness of intermittent treatment.

Methods and analysis A total of 140 patients diagnosed with NB MAC-LD in Japan will be randomly assigned, in a 1:1 ratio, to intermittent treatment group or daily treatment group, and three-drug combination therapy with clarithromycin, rifampicin and ethambutol will be continued for 1 year. The primary endpoint is the proportion of patients requiring modification of the initial treatment regimen. Secondary endpoints are adverse events, sputum culture conversion, time to sputum culture conversion, improvement of chest CT findings, change in health-related quality of life score and development of clarithromycin resistance.

Ethics and dissemination This trial was approved by the National Hospital Organisation Review Board for Clinical Trials (Headquarters). The results of this study will be reported at a society meeting or published in a peer-review journal.

INTRODUCTION

Recently, the worldwide incidence of pulmonary infection with non-tuberculous mycobacteria (NTM), pulmonary non-tuberculous mycobacterial disease (pulmonary NTM disease), has rapidly increased. In Japan,

the incidence of pulmonary NTM disease in 2014 was 14.7 per 100 000 person-years, exceeding the incidence of culture-positive tuberculosis and being relatively higher than that in Europe and the USA.¹ *Mycobacterium avium* complex (MAC)-lung disease (LD) accounts for approximately 90% of pulmonary NTM disease cases in Japan. The disease type is classified into fibrocavitary (FC) and nodular/bronchiectatic (NB) types. In particular, the incidence of NB MAC-LD has rapidly increased in middle aged and elderly Asian women without underlying diseases. A recent study clarified that NB types with cavitary lesion (cavitary NB) had treatment outcomes more similar to FC types than noncavitary NB types, and subdivided NB MAC-LD into the cavitary NB form and noncavitary NB form.²

The standard treatment for MAC-LD is three-drug combination therapy with rifampicin, ethambutol and clarithromycin or azithromycin, with the addition of an aminoglycoside for the first 2–3 months in severe cases. This regimen was established by applying the results of several randomised controlled studies involving patients with disseminated MAC disease, which frequently occurred in the end stage of HIV infection, to MAC-LD treatment; clinical evidence for MAC-LD is insufficient.³ Treatment outcomes of the standard treatment with three drugs are relatively poor regarding both treatment success and default rates.^{4–6} Adverse reactions, such as gastrointestinal symptoms and visual disorder, require dose reduction

or discontinuation, raising the important issue of poor tolerance.

According to official statements by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA),⁷ intermittent treatment involving three-times-a-week administration is recommended as the initial standard treatment for NB MAC-LD, excluding severe-status cases. For patients with severe status including cavitory disease, those with recurrence, and those with FC MAC-LD, daily treatment is recommended because intermittent treatment for such patients is less effective.⁸ In the British Thoracic Society (BTS) guidelines,⁹ intermittent treatment involving three-times-a-week administration is also recommended for non-cavitory mild-status patients, and daily treatment is recommended for severe-status patients. On the other hand, intermittent treatment was not described in an official announcement by the Japanese Society for Tuberculosis,³ and daily treatment regimens were recommended for all disease types; there is no consensus about intermittent treatment for MAC-LD in Japan. Thus, currently, the standard treatment for NB MAC-LD, excluding severe-status patients, differs between Japan and other countries.

Based on the results of studies conducted by Wallace *et al*¹⁰ and Jeong *et al*,¹¹ intermittent treatment is considered

more tolerable than daily treatment and its efficacy may be similar to that of daily treatment in patients with non-cavitory NB MAC-LD. However, these were single-centre, retrospective studies. No randomised controlled study directly comparing intermittent treatment with daily treatment has been performed to date.

The purpose of this study is to compare the safety and efficacy by randomly assigning subjects to receive intermittent or daily treatment for non-cavitory NB MAC-LD in Japan and to investigate the usefulness of intermittent treatment.

METHODS AND ANALYSIS

Trial design

This is a multicentre, open-label, randomised controlled study. Eighteen medical institutions in Japan will participate.

This trial was registered in the Japan Registry of Clinical Trials (jRCT): jRCTs031190008.

Participants

Patients who meet the eligibility criteria presented in [box 1](#) will be enrolled in this study.

Box 1 Eligibility criteria

Inclusion criteria

1. Nodular/bronchiectatic MAC lung disease meeting the 2007 ATS/IDSA criteria.
2. Treatment naive for MAC lung disease.
3. Without a cavity on chest CT regardless of size.
4. No serious symptoms (fever (38°C or higher), dyspnoea (mMRC dyspnoea score ≥ 2) or active haemoptysis).
5. Patients who were considered to be eligible for the start of treatment based on clinical findings by the attending physician.
6. Aged 20–79 years (on the day of informed consent).
7. Body weight ≥ 30 kg
8. ECOG PS of 0–2.
9. Maintained organ function and laboratory data at the time of registration meeting the following criteria:
 - A. Neutrophil count: $\geq 500/\text{mm}^3$.
 - B. AST and ALT: less than or equal to threefold of the upper limit of the institutional normal range.
 - C. Total bilirubin: less than or equal to twofold of the upper limit of the institutional normal range.
 - D. Creatinine: less than or equal to twofold of the upper limit of the institutional normal range.
10. Written informed consent

Exclusion criteria

1. Highly resistant to clarithromycin (MIC: ≥ 32) on a drug sensitivity test.
2. HIV antibody-positive.
3. Disseminated MAC disease.
4. Cystic fibrosis.
5. Active tuberculosis and other serious complications (malignant tumors, unstable angina, myocardial infarction or psychiatric diseases that are difficult to control).
6. Pregnant women or those who may become pregnant.
7. History of hypersensitivity to clarithromycin, rifampicin or ethambutol.
8. Receiving drugs contraindicated for combination with clarithromycin or rifampicin.
9. Avoidance of starting ethambutol suggested based on ophthalmological examination during the screening period.
10. QT prolongation (QTc: ≥ 450 ms) on electrocardiography at the time of screening.
11. Patients who were considered to be ineligible for participation in this study by the study investigators.

ALT, alanine aminotransferase; AST, aspartate transaminase; ATS/IDSA, American Thoracic Society and Infectious Diseases Society of America; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MAC, Mycobacterium avium complex; MIC, minimum inhibitory concentration; mMRC, modified Medical Research Council.

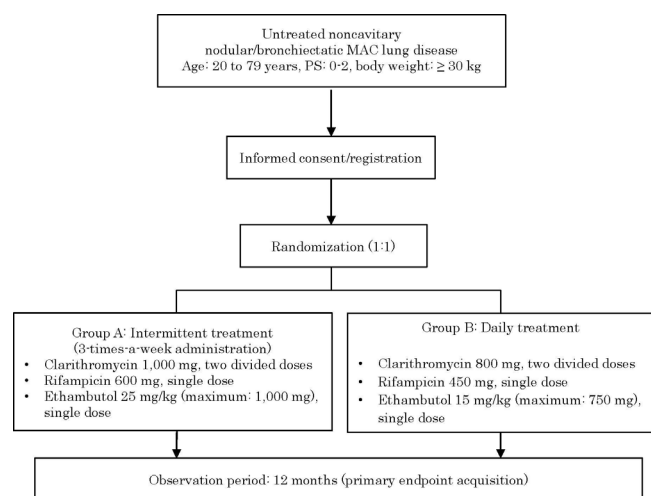


Figure 1 Outline of this study. MAC, *Mycobacterium avium* complex.

Interventions

The outline and exact schedule of this study are shown in figures 1 and 2, respectively. Combination therapy with clarithromycin, rifampicin and ethambutol will be continued for 1 year. In Japan, azithromycin is not approved for the treatment of MAC disease. The details of treatment in each group are shown below. We set the doses of the study drugs within the range approved in Japan, referring to the guidelines of ATS/IDSA⁷ and BTS.⁹ Those doses are the same as or lower than that suggested in the guidelines. Administration at the same total daily doses will not be regarded as a modification of treatment.

Group A: intermittent treatment group

At the following daily doses, these drugs will be orally administered three times a week:

- ▶ Clarithromycin, 1000 mg, two divided doses.
- ▶ Rifampicin, 600 mg, single dose.
- ▶ Ethambutol, 25 mg/kg, maximum 1000 mg (1000 mg for body weight ≥ 40 kg, 875 mg for 35 to <40 kg, 750 mg for <35 kg), single dose.

Group B: daily treatment group

At the following daily doses, these drugs will be orally administered every day:

- ▶ Clarithromycin, 800 mg, two divided doses.
- ▶ Rifampicin, 450 mg, single dose.
- ▶ Ethambutol, 15 mg/kg, maximum 750 mg (750 mg for body weight ≥ 50 kg, 625 mg for 40 to <50 kg, 500 mg for body weight <40 kg), single dose.

Endpoints

The primary endpoint is the proportion of patients changing the initial treatment regimen.

The secondary endpoints are the incidence of adverse events, proportions of patients with sputum culture conversion, time to sputum culture conversion, amelioration of thoracic CT findings, change in health-related quality of life (QOL) score and development of clarithromycin resistance.

Concerning the primary endpoint, the criteria for changing the initial treatment regimen are shown in box 2. The severity of adverse events will be evaluated using the Common Terminology Criteria for Adverse Events V.4.0. Even if the doses of one, two or all drugs are reduced, or even if administration is discontinued, initial-dose recovery within 4 weeks will not be regarded as regimen modification as the primary endpoint.

Regarding the sputum culture conversion, sputum acid-fast bacilli (AFB) culture in an automated mycobacterial growth indicator tube system (Becton Dickinson) will be conducted 1, 3, 6, 9 and 12 months after the start of the study treatment and we define a case with at least three consecutive negative AFB culture and maintaining negative until 12 months, as culture conversion. The date of culture conversion is defined as the sampling date of the first negative culture. In calculation of the proportions, the following two formulae will be used: patients with negative conversion in the absence of regimen modification/all sputum culture-positive patients and patients achieving negative conversion regardless of the presence of regimen modification/all sputum culture-positive patients. Patients without positive sputum culture within 6 months before treatment will be excluded from the analysis. If sputum self-expectoration is difficult, sputum will be induced using nebulised hypertonic saline. If sputum expectoration is impossible despite the use of this method, the sputum will be regarded as culture negative.

With respect to the improvement rating of the imaging findings, chest X-ray and CT findings before the start of

Time Point (months)	Study Period						
	Enrollment	Randomization	Post-Randomization				
			1	3	6	9	12
ENROLLMENT:							
Informed consent	X						
Eligibility screen	X						
Randomization		X					
INTERVENTIONS:							
Intermittent treatment							
Daily treatment							
ASSESSMENTS:							
Demography	X						
Spirometry test	X						
Sputum examination	X		X	X	X	X	X
Anti-glycopeptidilipid-core IgA antibody	X						X
Chest X-ray	X						X
Chest CT	X						X
QOL	X						X
Clinical Laboratory test	X		X	X	X	X	X
Ophthalmological examination	X		X	X	X	X	X
ECG	X		X	X	X	X	X
Treatment adherence			X	X	X	X	X
AE							

Figure 2 Schedule of enrolment, interventions and assessments during the study. AE, adverse event; QOL, quality of life

Box 2 Criteria for changing the initial treatment regimen

- ▶ Ophthalmologist's decision to discontinue ethambutol (discontinued ethambutol that cannot be resumed).
- ▶ Platelet count decrease of grade 3 or more (all drugs discontinued and rifampicin cannot be resumed).
- ▶ Peripheral neuropathy of grade 2 or more (ethambutol stopped and cannot be resumed).
- ▶ QT prolongation (QTc >500 ms) (clarithromycin stopped and cannot be resumed).
- ▶ Any AE of grade 4 or higher (stop all drugs).
- ▶ Drug interruption, dose reduction or change from daily to intermittent administration that cannot be returned to the initial treatment regimen even after more than 28 days.
- ▶ Judged difficult to continue the study treatment by the principal investigator.
- ▶ Increasing doses of study treatment, change from intermittent to daily administration, surgery or addition of drugs other than the study treatment for reasons including exacerbation of the original disease.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; MAC, Mycobacterium avium complex

the study treatment and after 12 months will be classified into three groups through blind-assessment-based central evaluation: improvement, no change and deterioration. The proportions of patients achieving 'improvement' will be compared.

For the change of health-related QOL scores, changes after 12 months from the baseline score evaluated using St. George's Respiratory Questionnaire and 36-Item Short Form Survey will be assessed.

Regarding the development of clarithromycin resistance, the proportions of patients with development of clarithromycin resistance at least once after the start of the study treatment will be compared.

Sample size

Based on the results of a retrospective, observational study in patients with NB MAC-LD,¹¹ we determined the regimen modification proportions in the daily treatment group and intermittent treatment group to be 42% and 19%, respectively. Sample size was calculated as 62 per group, given a one-sided significance level of 2.5% and statistical power of 80% to detect a reduction in drug proportions in the intermittent treatment group. Taking dropouts into account, the sample size has been set at 70 per group (140 patients in total).

Randomisation

Subjects will be assigned to each group with equal probability using the electronic data capture (EDC) system. The minimisation method will be adopted for randomisation. As balancing factors for randomisation, the medical institutions, sputum culture testing results (positive, negative) and body weight (<50 kg, ≥50 kg) will be used.

Blinding

This is an open-label clinical study and blinding will not be adopted. Regarding 'the modification of the initial treatment regimen due to adverse events' as the primary endpoint, criteria for changing the treatment regimen were clearly defined to avoid a bias related to different persons responsible for evaluation.

Data collection and monitoring

An EDC system will be used in the present study. Study investigators or those designated as such use strictly controlled personal electronic signatures (IDs and passwords) to login to the EDC system. Collected patient information is promptly entered into the EDC system and sent to a data centre. Transmitted electronic data are treated as case report forms. Study investigators or those designated as such perform all data entry and corrections. They can make inquiries within the EDC system as necessary, as well as respond to inquiries created by data managers and other staff. Study investigators confirm the accuracy of all data input.

This trial will employ centralised monitoring based on data collected via the EDC system; no on-site monitoring will be performed in principle. Monitoring consists of checking data as necessary, and individual facilities may be contacted to add/enter any missing data. Periodic monitoring will be carried out once yearly.

Statistical methods

A population, excluding patients violating the study protocol (no acquisition of written informed consent, serious violations on study procedures) from all registered patients, will be regarded as a full analysis set (FAS). A population, excluding patients violating eligibility/exclusion criteria in the study protocol, such as study treatment and combination therapy, those with poor compliance (compliance during protocol treatment <75%), and those with contraindicated drugs/therapies from the FAS, will be regarded as a per-protocol set (PPS). Efficacy will be primarily analysed using the FAS. For the primary endpoint, we will additionally analyse data in the PPS. A population, excluding those for whom the study treatment was not performed from all registered patients, will be regarded as the population to be analysed for safety.

In the analysis of the primary endpoint, logistic regression analysis using allocation factors excluding medical institutions as covariates will be used to compare the groups.

In the analysis of the secondary endpoints, dichotomous or categorical variables will be analysed using

Fisher's exact test. Regarding continuous data, summary statistics will be presented, and the distribution of data will be confirmed. If data follow a normal distribution, the two-sample t-test or analysis of covariance will be performed. If transformed variables do not follow a normal distribution, they will be compared between two groups using Wilcoxon's rank sum test. The incidence of each adverse event in each group will be calculated, and Fisher's exact test will be performed.

A two-sided $p < 0.05$ will be considered statistically significant. No interim analysis will be conducted in this study.

Patient and public involvement

There were no patients or public involvement in the development of this trial.

DISCUSSION

Few randomised controlled trials have been conducted to evaluate the benefits of standard therapy in patients with MAC-LD. In this study, we focused on limited evidence for an advantage of intermittent therapy of non-cavitary NB MAC-LD.

In standard therapy in NB MAC-LD in Japan, low tolerability is a major problem. Treatment is not easily initiated due to concerns about side effects. Moreover, even if treatment is started, it is often stopped due to side effects, and patients are hesitant to resume it afterwards. It is expected that intermittent treatment will help to overcome such disadvantages.

The inclusion of ethambutol in macrolide-based treatment is considered to be critical for preventing the development of poor-prognostic macrolide-resistant MAC disease.^{12 13} Previous retrospective studies reported that intermittent treatment has a low discontinuation rate of ethambutol,^{10 11} and intermittent treatment may also reduce the macrolide resistance that can occur after the discontinuation of ethambutol.

If the safety and efficacy of intermittent treatment could be confirmed in this clinical trial, a new standard therapy in Japan would be established. We believe that both side effects and drug costs can be reduced, resulting in an improvement of patients' QOL as well as lower medical expenses. To the best of our knowledge, this is the first study to compare the impact on health-related QOL between intermittent and daily therapy for MAC-LD. The Japanese government set a goal to reduce the amount of antimicrobial use in the 'National Action Plan on Antimicrobial Resistance',¹⁴ and intermittent treatment is expected to contribute to the reduction in macrolide antibacterial drug use.

ETHICS AND DISSEMINATION

Ethics

The present study complies with the World Medical Association's Declaration of Helsinki, Clinical Trials Act and Act on the Protection of Personal Information. It was

approved by the National Hospital Organisation Review Board for Clinical Trials (Headquarters) in February 2019. Prior to participation in the study, patients must have the study fully explained to them by a study investigator or research team member using an explanation document and consent form, and they must provide written consent.

Safety reports

Information on all severe adverse events from the start of the study treatment until final observation or discontinuation will be collected. After the initial reporting of a severe adverse event, the principal investigator or attending physicians will trace it until there is a definitive assessment of the event (death, recovery or inability to trace). If an unexpected, severe adverse event associated with this study occurs, the study representative must report it to the Minister of Health, Labour and Welfare, and publish the status of its management and outcome on the homepage of the study representative's institution.

Dissemination plan

The results of this study will be reported at a society meeting or published as an article within 2 years of the study completion.

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Contributors TN conceived the study and participated in its design and coordination. HH participated in the design of the study and is responsible for the statistical analysis plan. MY, YK, MS, KO and YI participated in the establishment of the study design. AMS is responsible for data management and central monitoring. The study protocol was developed by all the authors of this manuscript. All authors read and approved the final version of the manuscript.

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