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Original Article

The association between erythromycin monotherapy for *Mycobacterium avium* complex lung disease and cross-resistance to clarithromycin: A retrospective case-series study

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ABSTRACT

Long-term, low-dose erythromycin monotherapy, based on the anti-inflammatory effects of macrolides, has been reported to have the potential to suppress the exacerbation of Mycobacterium avium complex (MAC) lung disease with less toxicity. It remains unclear whether erythromycin monotherapy induces cross-resistance to clarithromycin, a key drug for MAC. To clarify this point, we conducted a retrospective, single-center, case-series study on patients with MAC lung disease who underwent erythromycin monotherapy for at least 6 months. Drug susceptibility tests, before and after erythromycin treatment initiation, were analyzed. Thirty-three patients were included in our study. All 33 patients showed susceptibility to clarithromycin for MAC both before and after erythromycin monotherapy. There was no significant difference in clarithromycin minimum inhibitory concentrations between before and after erythromycin treatment (median difference = 0 μg/ml; $P = .313$, Wilcoxon's signed-rank test). We conclude that erythromycin monotherapy for MAC lung disease may not induce cross-resistance to clarithromycin.

1. Introduction

Mycobacterium avium complex (MAC) can cause chronic and progressive lung infection, and MAC lung disease (MAC-LD) is increasing worldwide [1,2]. Although multidrug chemotherapy, including clarithromycin, is the standard treatment for MAC-LD, this requires a long treatment period and often causes drug-related toxicities. The efficacy of standard therapy is not sufficient to cure MAC-LD completely, but rather, is mainly prescribed to suppress exacerbation in clinical practice. Moreover, some patients with MAC-LD show a long-term stable or slowly progressive course without intensive chemotherapy. For these reasons, the timing of multidrug chemotherapy initiation is controversial. For mild MAC-LD patients, treatments less intensive than the standard multidrug treatment, and alternative, well-tolerated chemotherapies may be useful to control symptoms and suppress exacerbation for MAC-LD in clinical practice.

Macrolides have anti-inflammatory effects and are often used to treat chronic pulmonary inflammatory diseases such as diffuse panbronchiolitis, cystic fibrosis, asthma, bronchiectasis, and chronic obstructive pulmonary disease, conferring beneficial effects to patients [3–5]. A retrospective study reported that long-term, low-dose erythromycin monotherapy may potentially suppress the exacerbation of MAC-LD, with well-tolerated adverse events [6].

To date, clarithromycin and azithromycin are the only antimicrobial agents demonstrated to be effective in treating MAC-LD, both in vitro and in clinical practice [7]. Macrolides are known to produce cross-resistance among pathogens such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Helicobacter pylori* [8–10]. A randomized prospective study among MAC patients with autoimmune deficiency syndrome (AIDS) treated by clarithromycin monotherapy showed that 46% of these patients acquired resistance to clarithromycin 4 months after treatment [11]. Once MAC patients acquire clarithromycin-resistance, the treatment prognosis becomes

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poor [12]. Consequently, clarithromycin monotherapy is strictly prohibited. In contrast, erythromycin monotherapy is highly unlikely to induce cross-resistance to clarithromycin. A study reported that the rate of response to multidrug regimens after erythromycin monotherapy for MAC-LD was comparable to control patients naïve to erythromycin treatment [6]. Among them, 4 out of 31 patients showed susceptibility to clarithromycin after erythromycin monotherapy. Drug susceptibility tests after erythromycin monotherapy have not been widely investigated. It remains unclear whether the clarithromycin minimum inhibitory concentrations (MICs) for MAC after erythromycin treatment change.

Therefore, in the present study, we aimed to clarify whether erythromycin monotherapy for MAC-LD induces cross-resistance to clarithromycin, by reviewing the clarithromycin MICs for MAC reported before and after erythromycin monotherapy in a select group of Japanese patients.

2. Patients and methods

2.1. Study subjects

A retrospective, single-center, case-series study was conducted between July 2008 and April 2017 at the Department of Respiratory Medicine, National Hospital Organization, National Toneyama Hospital (Osaka, Japan). The study included patients who met the diagnostic criteria for MAC-LD of the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) of 2007, and had received oral erythromycin monotherapy for at least 6 months. Moreover, patients who twice received drug susceptibility exams were selected for this study. The first drug susceptibility test was performed immediately before or after the initiation of erythromycin monotherapy. The timing of the second drug susceptibility test was dependent on each clinical physician, so this was not uniform. However, exams were performed during erythromycin monotherapy, or soon after discontinuation of treatment. Patients were excluded from the analysis if they did not receive drug susceptibility tests twice, if the interval between tests was less than 6 months, or if they showed resistance to clarithromycin upon the first test (Fig. 1). The study was approved by the National Hospital Organization, National Toneyama Hospital Review Board (approval number 1721). The approval allowed retrospective data collection and reporting of anonymous results; thus, informed consent was not obtained from eligible study subjects.

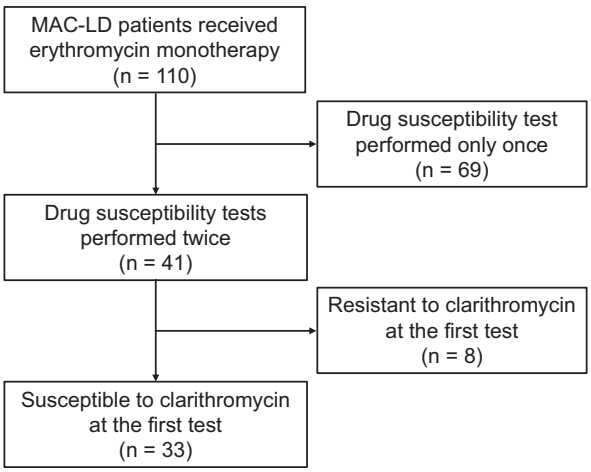

Fig. 1. Flow diagram of subjects included in the study. MAC-LD = *Mycobacterium avium* complex lung disease.

2.2. Microbiological and drug susceptibility examinations

Expectorated sputum or samples collected via bronchoscopy were examined by fluorescent staining, and culture examination for acid-fast bacilli was performed using the conventional methods of 2% Ogawa egg medium (Japan BCG, Tokyo, Japan), or a mycobacteria growth indicator tube (Japan Becton, Dickinson and Company, Tokyo, Japan). Drug susceptibility tests were performed with the macrolide susceptibility kit (BrothMIC NTM, Kyokuto Pharmaceutical Industrial, Tokyo, Japan).

2.3. Outcomes and definitions

The main outcome included evaluation of susceptibility to clarithromycin for MAC at the second drug susceptibility test, and differences of MICs between the first and second drug susceptibility tests. We categorized clarithromycin minimum inhibitory concentration (MIC) $\leqq$8 μg/mL, 16 μg/mL and $\geq$32 μg/mL as susceptible, intermediate, and resistant, respectively [13].

We compared chest radiographs taken at the first and second drug susceptibility tests to evaluate the efficacy of erythromycin monotherapy for MAC-LD. Chest findings were assessed by two respiratory physicians without prior knowledge of the clinical data. We categorized radiographs into 3 groups: improved, stable, and exacerbated. Moreover, we observed whether standard chemotherapy was performed after exacerbation of MAC-LD.

2.4. Statistical analysis

Statistical analysis was performed using Graph-Pad Prism Version 7 (GraphPad Software, Inc., San Diego, CA, USA). Continuous variables were compared using the Wilcoxon's signed-rank test. The Fisher's exact test was used to compare categorical variables. $P < .05$ was regarded as statistically significant.

3. Results

3.1. Enrolment of study subjects and characteristics

A total of 110 MAC-LD patients received erythromycin monotherapy at a dose of 200–600 mg/day for more than 6 months during the study period. Of them, 41 patients were tested twice for drug susceptibility to clarithromycin for MAC. Among them, 8 patients were excluded because they showed resistance to clarithromycin at the first drug susceptibility test. Ultimately, 33 patients were investigated (Fig. 1). The baseline characteristics of the study subjects are shown in Table 1. Nineteen patients received erythromycin monotherapy as an initiation treatment, 4 received as subsequent standard chemotherapy, and 10 received as subsequent other treatments. Data regarding body mass index were lacking in 12 patients because their heights and weights could not be collected from medical records.

3.2. Drug susceptibility to clarithromycin and variation of MICs

The median interval of drug susceptibility tests was 24 months (interquartile range (IQR): 12–36 months). All 33 patients showed susceptibility to clarithromycin both before and after erythromycin monotherapy. The median clarithromycin MICs before and after erythromycin monotherapy were 0.25 μg/ml (IQR: 0.25–0.44 μg/ml) and 0.25 μg/ml (IQR: 0.125–0.50 μg/ml), respectively. We found no statistically significant differences of MICs between the first and second tests (median difference = 0 μg/ml; $P = .313$) (Fig. 2). The number of variations of clarithromycin MICs for MAC were as follows: MICs increased in 6 patients; were unchanged in 11 patients;

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