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Original Article

The clinical efficacy of a clarithromycin-based regimen for *Mycobacterium avium* complex disease: A nationwide post-marketing study

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ABSTRACT

The revised 2007 American Thoracic Society/Infectious Diseases Society of America statement recommend clarithromycin-based combination therapy for treatment of *Mycobacterium avium* complex lung disease and stipulates approximately 1 year of continuous treatment after bacilli negative conversion. However, supporting data are insufficient. Our objective was to obtain data on the clinical outcome of clarithromycin-based daily regimens by conducting a nationwide retrospective post-marketing study of *M. avium* complex lung disease. In accordance with the Japanese guidelines, patients were enrolled in this survey according to their chest radiographic findings and microbiologic test results. They were treated with a multidrug regimen including clarithromycin, rifampicin, and ethambutol (clarithromycin-based regimen) until bacilli negative conversion, and the treatment was continued for approximately 1 year after the initial conversion. Data were collected before administration, at the time of bacilli negative conversion, at the end of treatment, and at 6 months after the end of treatment. Of the 466 subjects enrolled in the study, 271 patients who received clarithromycin at 800 mg/day underwent evaluation for *M. avium* complex disease. The final bacilli negative conversion rate in those patients was 94.7%. The bacteriological relapse rate was 5.0% (5/100 patients). Bacteriological relapse was noted in patients treated for less than 15 months after conversion. No life-threatening or serious adverse drug reactions were observed. This study demonstrated that a clarithromycin-based daily regimen can yield a high bacteriological conversion rate in *M. avium* complex disease. After conversion, treatment for less than 15 months might be insufficient to prevent bacteriological relapse.

1. Introduction

The incidence of *Mycobacterium avium* complex (MAC) lung disease is increasing worldwide [1–7], and MAC lung disease is being routinely encountered in medical practice in Japan as well [8]. The American Thoracic Society and the Infectious Disease Society of America published an official statement (ATS/IDSA statement) for the treatment of nontuberculous mycobacterial lung disease in 2007 [9]; these were followed by the publication of guidelines with almost the same content, by the Japanese Society for Tuberculosis and the Japanese Respiratory Society entitled "Guidelines for the Diagnosis of Pulmonary Nontuberculous Mycobacterial Disease-2008" and "Guidelines for Chemotherapy of Pulmonary Nontuberculous Mycobacterial Disease-2012 Revised Version" [10,11], respectively. Since the approval (in August 2008) of MAC lung disease as an additional insurance-covered indication for the use of clarithromycin (CAM), Japanese standard chemotherapy regimens for pulmonary MAC disease are based on triple therapy with rifampicin (RFP: maximum 600 mg/day, once daily), ethambutol (EB: maximum 750 mg/day, once daily) and CAM (600–800 mg/day, once or twice daily).

The ATS/IDSA statement recommended a thrice-weekly (macrolide-based) regimen for patients with noncavitary, nodular,

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bronchiectatic-type MAC lung disease. Although the effectiveness of such a regimen, primarily based on azithromycin (AZM), has only recently been reported in Korea [12], the area and sample size investigated have been small in terms of therapeutic outcome, and therefore evidence is limited. Additionally, there are limited data from clinical trials in Japan and other countries regarding the effectiveness and tolerability of a long-term CAM-based daily regimen for MAC lung disease.

Therefore, we conducted a nationwide retrospective study as a postmarketing survey on the use of CAM for MAC lung disease in areas throughout Japan. The objective of this study was to validate the CAM-based daily regimen stipulated in the guidelines and to provide supporting data by clarifying (1) Japanese patient characteristics, (2) the bacilli negative conversion rate depending on the CAM-based combination therapy, (3) the rate of bacteriological relapse depending on the duration of treatment after the initial bacilli negative conversion, and (4) the tolerability of long-term CAM-based therapy.

2. Patients and methods

2.1. Overview of the study

This study was conducted from October 2008 to September 2013 at 130 medical facilities with departments specializing in the treatment of respiratory or mycobacterial infection in Japan.

In accordance with the ATS/IDSA statement and Japanese guidelines, patients meeting all of the following inclusion criteria were enrolled in the study: (1) symptoms that are characteristic of MAC lung disease or that could be clearly differentiated from those of other diseases, (2) chest radiographic findings allowing the exclusion of preexisting lung diseases or other diseases, and (3) positive culture results from at least two separate expectorated sputum samples or one bronchoalveolar lavage fluid sample.

Exclusion criteria were as follows: other than MAC lung disease; results and other data not collected during the period of this study; treatment discontinued because of other diseases; CAM treatment for less than 30 days; and CAM administration at doses other than 800 mg/day, because the purpose of the study was to validate the standard 800-mg CAM-based daily regimen in Japan.

Patient data were collected before the start of treatment (evaluation period: 3 months before the start of treatment to Day 0), at the time of bacilli negative conversion (evaluation period: the first day of bacilli negative conversion to 3 months after that date), at the end of treatment (evaluation period: the last day of CAM treatment to 3 months after that date), and 6 months after the end of treatment (evaluation period: 6–9 months after the end of CAM treatment). Collected data included the following: bacterial test results (sample name, microscopic examination of sputum smear, culture, polymerase chain reaction [PCR], bacterial count, minimum inhibitory concentration [MIC]); physical examination (temperature, cough strength, sputum characteristics, presence of bloody sputum, general malaise, breathlessness, weight); blood sample parameters (white blood cell [WBC] count, C-reactive protein [CRP]), renal function and liver function tests; and chest radiography, including chest X-ray and HRCT images (shadow diffusion, image findings; when CT was used, the image was read in the same manner as that of X-ray). Clinical efficacy was evaluated by reference to the criteria for respiratory tract infection set by the Japanese Society of Chemotherapy [13]. Patients were classified into the following categories, based on subjective and objective symptoms, chest image interpretation, and bacterial test results, evaluated at the start and end of treatment: “improved”, when improvement was observed in all three items “unchanged”, when improvement was not observed in 2 or more items “aggravated”, when aggravation was observed in 1 or more items and “undeterminable”, when assessment of the items was challenging. If cases did not correspond to any of the above evaluation criteria, the reasons were described in the survey slip and whether or not these cases would be included was decided at a later date after the coordinating investigators (authors) reviewed the appropriateness of the evaluation.

Two disease types were classified: “fibrocavitary-type disease” and “nodular bronchiectatic-type disease.” A case was judged as fibrocavitary-type disease, when cavity shadows and fibrosis were identified by the primary physician, based on chest image findings at the start of treatment, and related clinical conditions were observed. A case was defined as nodular bronchiectatic-type disease, when micronodular shadows and bronchodilatation were mainly identified, and related clinical conditions were observed. Chest image findings and shadow diffusions at the start of treatment were classified into three levels of involvement (within one lobe, more than one lobe, at least one entire lung) for evaluation. The following criteria were used for evaluation of shadow diffusion during the period from the start to the end of treatment: “improved” for cases with improvement by one or more level, “unchanged” for cases with no improvement, “aggravated” for cases with aggravation by one or more level, and “undeterminable” for cases in which evaluation was difficult. For the latter cases, the reasons were described in the survey slip.

All adverse events reported during treatment with CAM were included in the analysis, regardless of any relationship with CAM; those considered to be related to CAM were included as adverse drug reactions, and were assessed on the basis of Criteria for Safety Evaluation of Antimicrobial Agents [14]. Adverse events were coded according to ICH MedDRA (version 17.0).

This study was conducted as a post-marketing survey after the Japanese Pharmaceuticals and Medical Devices Agency pointed out a lack of sufficient information about the efficacy of recommended regimens. The study was carried out in compliance with the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) in Japan, which required neither acquisition of informed consent from enrolled patients nor ethical review by a medical institution. We conducted this survey in accordance with the ministerial ordinance on GPSP regarding data handling, self-monitoring, payment or receipt of money, and release of information.

2.2. Drug regimen

Although the ATS/IDSA statement recommend the option of an intermittent, thrice-weekly regimen for patients with nodular bronchiectatic-type disease, a CAM-based daily regimen has been recommended in Japan [15–18]. Thus, a CAM-based daily regimen was selected for the patients enrolled in this study, since some patients might have fibrocavitary-type disease.

CAM was orally administered at 800 mg/day and a three-drug regimen including RFP, EB, and CAM was selected. As a general rule in accordance with the guidelines, treatment was continued for approximately 1 year after the initial bacilli negative conversion [9–11].

2.3. Efficacy and safety variables

The primary endpoint of this study was the bacilli negative conversion rate in patients with MAC lung disease. Primary physicians periodically conducted bacterial tests (one or more times a month) after the start of treatment with CAM. When sputum samples could be collected from patients and two consecutive sputum culture results were negative, the first date of these tests