Clofazimine-Containing Regimen for the Treatment of *Mycobacterium abscessus* Lung Disease

Bumhee Yang,a Byung Woo Jhun,a,b Seong Mi Moon,a Hyun Lee,a Hye Yun Park,a Kyeongman Jeon,a Dae Hun Kim,a Su-Young Kim,a Sung Jae Shin,c Charles L. Daley,d Won-Jung Koha

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Division of Pulmonary, Allergy and Critical Care Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, South Korea; Department of Microbiology and Brain Korea 21 PLUS Project for Medical Science, Yonsei College of Medicine, Seoul, South Korea; Division of Mycobacterial and Respiratory Infections, Department of Medicine, National Jewish Health, Denver, Colorado, USA.

ABSTRACT Patients with lung disease caused by *Mycobacterium abscessus* subsp. *abscessus* (here *M. abscessus*) typically have poor treatment outcomes. Although clofazimine (CFZ) has been increasingly used in the treatment of *M. abscessus* lung disease in clinical practice, there are no reported data on its effectiveness for this disease. This study sought to evaluate the clinical efficacy of a CFZ-containing regimen for the treatment of *M. abscessus* lung disease. We performed a retrospective review of the medical records of 42 patients with *M. abscessus* lung disease who were treated with CFZ-containing regimens between November 2013 and January 2015. CFZ was administered in combination with other antibiotics as an initial antibiotic regimen in 15 (36%) patients (initial treatment group), and it was added to an existing antibiotic regimen for refractory *M. abscessus* lung disease in 27 (64%) patients (salvage treatment group). Overall, there was an 81% treatment response rate based on symptoms and a 31% response rate based on radiographic findings. Conversion to culture-negative sputum samples was achieved in 10 (24%) patients after CFZ-containing antibiotic treatment, and during treatment, there were significant decreases in the positivity of semi-quantitative sputum cultures for acid-fast bacilli in both the initial (*P* = 0.018) and salvage (*P* = 0.001) treatment groups. Our study suggests that CFZ-containing regimens may improve treatment outcomes in patients with *M. abscessus* lung disease and that a prospective evaluation of CFZ in *M. abscessus* lung disease is warranted.

KEYWORDS nontuberculous mycobacteria, *Mycobacterium abscessus*, clofazimine, treatment outcome

The prevalence of pulmonary disease caused by nontuberculous mycobacteria (NTM) is increasing worldwide (1, 2). The *Mycobacterium abscessus* complex is the most important cause of pulmonary infections by rapidly growing mycobacteria in patients with chronic lung diseases such as bronchiectasis and cystic fibrosis (3, 4). Currently, the *M. abscessus* complex can be divided into three subspecies: *M. abscessus* subsp. *abscessus* (here *M. abscessus*), *M. abscessus* subsp. *massiliense* (here *M. massiliense*), and *M. abscessus* subsp. *bolletii* (here *M. bolletii*) (5, 6). Among these three subspecies, *M. abscessus* is the most common pathogen (45 to 65%), followed by *M. massiliense* (20 to 55%) and *M. bolletii* (1 to 18%) (7).

*M. abscessus* is highly drug resistant. Guidelines from the American Thoracic Society and the Infectious Diseases Society of America recommend macrolide-based antibiotic therapy combined with intravenous amikacin (AMK) and either cefoxitin or imipenem, based on drug susceptibility testing (DST) (3). However, given the level of effectiveness...
of current antibiotic options (3), *M. abscessus* lung disease is considered a chronic, incurable infection for most patients, and the sputum culture conversion rates are low (8–12).

Clofazimine (CFZ) is a fat-soluble riminophenazine dye that was developed in the 1950s, mainly for use in the treatment of leprosy (13). This antimicrobial was recently introduced for the treatment of multidrug-resistant or extensively drug-resistant tuberculosis (14–17). Several reports have also reported the clinical efficacy of CFZ in the treatment of *Mycobacterium avium* complex lung disease (18–22); however, the results are inconsistent. Regarding *M. abscessus* infection, *in vitro* DST studies demonstrated a low MIC of CFZ and *in vitro* synergy between CFZ and other antibiotics, such as clarithromycin (CLR), AMK, or tigecycline (23–28). The antimycobacterial activity of CFZ against *M. abscessus* was also demonstrated *in vivo* with *Drosophila melanogaster* and mouse models of infection (29, 30).

CFZ has been increasingly used in the treatment of *M. abscessus* lung disease in clinical practice (31, 32). Moreover, the U.S. Cystic Fibrosis Foundation and the European Cystic Fibrosis Society recently recommended that the continuation phase of *M. abscessus* lung disease treatment should include a daily oral macrolide, inhaled amikacin, and two or three additional oral antibiotics, including CFZ (4). However, there are no reported data concerning the effect of CFZ on *M. abscessus* lung disease. Therefore, the purpose of this study was to evaluate the clinical efficacy and safety of a CFZ-containing regimen for the treatment of *M. abscessus* lung disease.

### RESULTS

#### Patient characteristics

The characteristics of the 42 patients with *M. abscessus* lung disease are shown in Table 1. The median patient age was 60 years, and most patients (79%) were female. Most patients (*n* = 36; 86%) had the nodular bronchiectatic form of *M. abscessus* lung disease. A total of 29 patients (69%) had positive acid-fast bacillus (AFB) sputum smears at the time of initiation of CFZ-containing antibiotic therapy.

CFZ was part of the initial treatment in 15 (36%) patients and was added as a salvage drug in 27 (64%) patients who had failed sputum culture conversion despite a median of 113.6 weeks (interquartile range [IQR], 51.2 to 232.4 weeks) of treatment with other antibiotics.

#### TABLE 1 Clinical characteristics of patients receiving clofazimine-containing antibiotic therapy

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Value (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yr) (IQR)</td>
<td>60 (53–69)</td>
</tr>
<tr>
<td>No. (%) of female patients</td>
<td>33 (79)</td>
</tr>
<tr>
<td>Median body mass index (kg/m²) (IQR)</td>
<td>20 (18–22)</td>
</tr>
<tr>
<td>No. (%) of nonsmokers</td>
<td>33 (79)</td>
</tr>
<tr>
<td>No. (%) of patients with underlying lung disease</td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>36 (86)</td>
</tr>
<tr>
<td>Previous tuberculosis</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Obstructive pulmonary disease</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Chronic pulmonary aspergilosis</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
</tr>
<tr>
<td>Median ESR level (mm/h) (IQR)</td>
<td>47 (24–79)</td>
</tr>
<tr>
<td>Median CRP level (mg/dl) (IQR)</td>
<td>0.57 (0.11–1.47)</td>
</tr>
<tr>
<td>No. (%) of patients with radiographic type</td>
<td></td>
</tr>
<tr>
<td>Nodular bronchiectatic form</td>
<td>36 (86)</td>
</tr>
<tr>
<td>With cavity</td>
<td>19</td>
</tr>
<tr>
<td>Without cavity</td>
<td>17</td>
</tr>
<tr>
<td>Fibrocavitary form</td>
<td>6 (14)</td>
</tr>
<tr>
<td>No. (%) of patients with positive sputum AFB smear</td>
<td>29 (69)</td>
</tr>
<tr>
<td>No. (%) of patients in initial treatment group</td>
<td>15 (36)</td>
</tr>
<tr>
<td>No. (%) of patients in salvage treatment group</td>
<td>27 (64)</td>
</tr>
</tbody>
</table>

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AFB, acid-fast bacillus.
For the 15 patients from the initial treatment group, 13 (87%) of the *M. abscessus* isolates had inducible resistance to CLR, and 2 (13%) were susceptible to CLR. For the 27 patients in the salvage treatment group, 23 (85%) of the *M. abscessus* isolates had inducible resistance to CLR, and 4 (15%) were resistant to CLR when the administration of CFZ began.

**Treatment.** The antibiotic regimens for the 42 patients are shown in Table 2. All patients received oral CFZ and a macrolide such as azithromycin (AZM) \( n = 41 \) or CLR \( n = 1 \). The median treatment duration of oral CFZ was 48.0 weeks (IQR, 24.8 to 48.0 weeks). All 15 patients in the initial treatment group received initial 4-week intravenous combination antibiotic therapy.

All 27 patients in the salvage treatment group had persistent positive cultures after at least 6 months of previous antibiotic therapy for *M. abscessus* lung disease, which had consisted of an oral macrolide (CLR \( n = 17 \); 63%; or AZM \( n = 19 \); 70%), oral fluoroquinolones (ciprofloxacin \( n = 5 \); 12% or moxifloxacin \( n = 4 \); 10%), and intravenous antibiotics, including AMK (\( n = 27 \); 100%), cefoxitin (\( n = 17 \); 63%), or imipenem (\( n = 10 \); 37%). In the salvage treatment group, 13 patients received 4 weeks of combination intravenous antibiotic treatment after rehospitalization, which included amikacin and cefoxitin (or imipenem) in addition to CFZ; the 14 remaining patients received CFZ in addition to the continuing oral regimen, such as oral macrolides (azithromycin or clarithromycin), in outpatient settings (Table 2).

Surgical resection, or lobectomy, was performed on three patients (one in the initial treatment group and two in the salvage treatment group) during the course of antibiotic treatment.

**Treatment responses after 12 months of a CFZ-containing regimen.** As shown in Table 3, there was an overall 81% treatment response rate based on symptoms and a 31% response rate based on radiographic findings. Although the level of symptomatic improvement appeared higher in the initial treatment group than in the salvage treatment group, the difference was not statistically significant (93% \( [14/15] \) versus 74% \( [20/27] \); \( P = 0.222 \)). Initial and 12-month follow-up high-resolution computed tomography (HRCT) images \( [n = 33] \) or chest radiographs \( [n = 9] \) were available for all patients. Radiologic improvement was notably greater in the initial treatment group than in the salvage treatment group (53% \( [8/15] \) versus 19% \( [5/27] \); \( P = 0.020 \)).

### Table 2 Antibiotics administered to the initial and salvage treatment groups

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients receiving treatment (%) ( (n = 42) )</th>
<th>Median duration of treatment (wk) (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofazimine</td>
<td>42 (100)</td>
<td>48.0 (24.8–48.0)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>28 (67)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0 (3.7–4.0)</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>19 (45)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.3 (1.1–4.0)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>9 (21)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.7 (1.4–3.6)</td>
</tr>
<tr>
<td>Macrolide</td>
<td>42 (100)</td>
<td>52.1 (44.5–52.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>All 15 patients in the initial treatment group received initial 4-week intravenous combination antibiotic therapy including amikacin and cefoxitin (or imipenem). Of the 27 patients in the salvage treatment group, 13 patients received 4-week combination intravenous antibiotic treatment after rehospitalization when clofazimine was added, and 14 patients received clofazimine in addition to the continuing oral regimen in outpatient settings.

### Table 3 Treatment responses after 12 months of treatment with a clofazimine-containing regimen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ( (n = 42) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of patients with symptomatic improvement</td>
<td>34 (81)</td>
</tr>
<tr>
<td>No. (%) of patients with radiologic improvement</td>
<td>13 (31)</td>
</tr>
<tr>
<td>Microbiologic improvement</td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients with sputum culture conversion</td>
<td>10 (24)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median time to negative culture conversion (wk) (IQR)</td>
<td>5.0 (4.6–28.9)</td>
</tr>
</tbody>
</table>

<sup)a</sup>Sputum negative culture conversion was achieved in 40% \( [6/15] \) of patients in the initial treatment group and in 15% \( [4/27] \) of patients in the salvage treatment group.
Sputum negative culture conversion was achieved in 10 (24%) patients after treatment with a CFZ-containing antibiotic (Fig. 1). The culture conversion rate was higher in the initial treatment group than that in the salvage treatment group, although the difference was not statistically significant (40% [6/15] versus 15% [4/27]; \( P = 0.128 \)). Within the salvage treatment group, the culture conversion rates did not differ between patients who started CFZ together with intravenous antibiotic treatment (2/13; 15%) and those who received CFZ in addition to the continuing oral regimen (2/14; 14%) (\( P = 0.936 \)). Figure 2 shows the results of serial testing (every 3 months) for sputum culture positivity, using solid media, after patients started a CFZ-containing regimen. During antibiotic treatment, sputum culture positivity trended lower in both the initial and salvage treatment groups, with statistically significant decreases being detected (\( P = 0.018 \) for the initial treatment group and \( P = 0.001 \) for the salvage treatment group).

**Adverse effects associated with CFZ.** During the treatment period, 23 (55%) patients experienced adverse effects from CFZ, resulting in either the discontinuation of the drug in 18 patients after 24.4 weeks (IQR, 17.2 to 40.8 weeks) of CFZ treatment or a dose reduction to 50 mg/day in 5 patients after 26.0 weeks (IQR, 17.7 to 36.2 weeks) of CFZ treatment (Table 4). Gastrointestinal disturbance was the most common cause of discontinuation (11 patients), and five patients discontinued CFZ due to reddish-brown skin discoloration.

![Image 1](http://aac.asm.org/) Cumulative sputum culture conversion rates after patients started a clofazimine-containing regimen.

**FIG 1** Cumulative sputum culture conversion rates after patients started a clofazimine-containing regimen.

![Image 2](http://aac.asm.org/) Serial changes in semiquantitative AFB sputum culture positivity on solid media after patients started a clofazimine-containing regimen. Vertical bars indicate the interquartile ranges.
DISCUSSION

In this study, we evaluated the clinical, radiologic, and microbiological responses of 42 patients with *M. abscessus* lung disease treated with CFZ-containing regimens. The most noticeable finding was that CFZ-containing regimens were moderately effective in treating *M. abscessus* lung disease. AFB culture conversion was achieved in 10 (24%) of the 42 study patients and in 6 (40%) of the 15 patients initially treated with CFZ. CFZ is primarily used to treat leprosy due to its lipophilicity in the skin and anti-inflammatory properties (13), but it has recently been applied for the treatment of drug-resistant tuberculosis (14–17). In mouse models of drug-susceptible and drug-resistant tuberculosis, lung culture conversion and relapse-free cure were obtained much earlier in mice treated with the CFZ-supplemented regimen than in those treated with the control standard regimen (33, 34). Moreover, previous studies reported that for treatment of mycobacterial diseases, CFZ has many advantageous characteristics such as a long half-life, slow metabolic elimination, the ability to achieve high concentrations in macrophages, rapid localization within phagocytes, and low cost (35–37). In addition, recent in vitro studies have shown that CFZ has significant synergistic activity when it is combined with AMK or CLR (23–28). Notably, a recent experimental study reported that CFZ prevented the regrowth of the *M. abscessus* type strain exposed to AMK and CLR (28). Although the experimental studies cited above suggest a potential role for CFZ in the treatment of NTM lung disease, several clinical studies evaluating the efficacy of CFZ for the treatment of *M. avium* complex lung disease reported inconsistent response rates (18–22), and clinical data on the outcomes of patients with *M. abscessus* lung disease treated with CFZ are extremely limited (31).

In our previous reports, sputum culture conversion rates ranged from 25% to 34% after 12 months of antibiotic treatment that did not include CFZ (8, 12). In another two studies in which the subspecies of the *M. abscessus* complex isolate causing *M. abscessus* lung disease was also identified, sputum culture conversion rates were 26 to 42% after long-term antibiotic therapy without CFZ (9, 11). In the present study, sputum culture conversion was achieved in 40% (6/15) of patients after antibiotic treatment that included CFZ from the start of the antibiotic regimen. Additionally, the sputum culture conversion rate seemed to be slightly higher (40%) when CFZ was used in combination with other antibiotics from the beginning of the treatment than the rates (25 to 34%) obtained in our previous studies in which we used almost the same antibiotic regimens and treatment duration, except for the exclusion of CFZ (8, 12); however, interpretations of the differing rates are difficult due to the small study population.

In the salvage treatment group, in which CFZ was added to the existing failing regimens, the sputum culture conversion rate was only 15% (15/27). However, the salvage treatment group was anticipated to be a more difficult group to treat in view of their previous and unsuccessful long-term antibiotic therapy. In addition, whereas 13% (2/12) of *M. abscessus* isolates were susceptible to CLR in the initial treatment group, no CLR-susceptible *M. abscessus* isolates were found in the salvage treatment group. In the present study, the salvage treatment group was defined as patients who had refractory *M. abscessus* lung disease, as indicated by persistent positive cultures after at least 6 months of antibiotic therapy. Because most patients with CLR-susceptible *M.

### TABLE 4 Adverse effects associated with clofazimine

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>No. (%) of patients</th>
<th>Discontinuation (n = 18)</th>
<th>Dose reduction (n = 5)</th>
<th>Total (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disturbance</td>
<td>11 (61)</td>
<td>1 (20)</td>
<td></td>
<td>12 (52)</td>
</tr>
<tr>
<td>Skin color change</td>
<td>5 (28)</td>
<td>4 (80)</td>
<td></td>
<td>9 (39)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td></td>
<td>1 (4)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (6)*</td>
<td>0 (0)</td>
<td></td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*This patient discontinued all antibiotics for *M. abscessus* lung disease, including clofazimine, after admittance to the intensive care unit due to severe pneumonia and sepsis.*

Clofazimine for Treatment of *M. abscessus* Lung Disease

*Antimicrobial Agents and Chemotherapy*

June 2017 Volume 61 Issue 6 e02052-16

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abscessus lung disease were successfully treated with macrolide-containing antibiotic regimens (12), the high CLR resistance rate in the salvage treatment group could be expected. However, this study demonstrated a significant decrease in the positivity of semiquantitative sputum cultures for AFB over the course of treatment with CFZ in both the initial treatment and salvage treatment groups, suggesting that CFZ-containing regimens can help to decrease the mycobacterial burden. Semiquantitative AFB culture positivity is likely to reflect disease burden and was used to assess microbiological responses to the treatment of NTM lung disease in some recently reported studies (38–40).

Given that M. abscessus lung disease is regarded as a chronic, incurable infection and that there are limited antibiotic options, improvement in the health-related quality of life is a reasonable treatment goal, especially in refractory cases (32). Therefore, in these contexts, administering an additional available oral agent, such as CFZ, which does not require the placement of an intravenous catheter, is a treatment strategy worth considering. Unfortunately, 43% (18/42) of our study patients discontinued CFZ during the course of treatment due to adverse effects such as gastrointestinal disturbance or skin discoloration. In recent studies, the two most commonly reported adverse effects of CFZ or CFZ-containing regimens were gastrointestinal disturbance and skin color change, which were reported in 14 to 89% of cases treated with CFZ for drug-resistant tuberculosis (41–43). In our study, patients who experienced gastrointestinal disturbances due to CFZ had nausea, vomiting, and abdominal discomfort, but there were no associated life-threatening gastrointestinal complications. Patients who experienced skin color changes did not have recurrent problems once the CFZ dose was decreased or discontinued. Although 43% of patients in our study discontinued CFZ due to side effects, the drug was relatively well tolerated, with no severe adverse effects.

This study had several limitations. First, this retrospective study included a relatively small sample of patients, and as it was not a controlled clinical trial, we did not have a control group for which CFZ therapy was omitted. Second, because we evaluated the treatment responses after 12 months of CFZ administration, long-term clinical and radiologic responses or maintenance of the conversion rate could not be evaluated. Third, because of its retrospective nature, data were not collected in a standardized fashion, especially for clinical symptoms and HRCT findings.

In conclusion, we evaluated the clinical, radiologic, and microbiological responses of 42 patients treated with CFZ-containing regimens for M. abscessus lung disease and found that these regimens were moderately effective. However, further evaluation of the clinical efficacy and adverse effects of long-term CFZ-containing regimens in patients with M. abscessus lung disease is needed.

MATERIALS AND METHODS

Study population. Consecutive patients with M. abscessus lung disease who received CFZ between November 2013 and January 2015 were identified from the NTM Registry of Samsung Medical Center (a 1,979-bed referral hospital in Seoul, South Korea), and their medical records were reviewed. CFZ has been available for the treatment of M. abscessus lung disease at our institution since November 2013. This retrospective study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB approval no. 2016-05-018). The patient information was anonymized and deidentified prior to analysis, and therefore, informed consent was waived.

A total of 42 patients with M. abscessus lung disease treated with a CFZ-containing regimen were identified. All of these patients fulfilled the diagnostic criteria for NTM lung disease (3), and they were divided into two groups based on the timing of the administration of CFZ. In the "initial treatment group," consisting of 15 patients (36%), CFZ had been administered from the start of the antibiotic regimen in conjunction with other antibiotics. In the "salvage treatment group," CFZ had been added to the existing regimen for 27 patients (64%) who had refractory M. abscessus lung disease, as indicated by persistent positive cultures after at least 6 months of antibiotic therapy. None of the patients had received CFZ prior to this study.

Radiographic and microbiological examination. Chest radiography and HRCT images were available at the time of CFZ-containing antibiotic treatment for all patients. The fibrocavitary form (previously called the upper lobe cavitary form) is defined by the presence of cavitary opacities, mainly in the upper lobes. The nodular bronchiectatic form is defined by the presence of bronchiectasis and multiple nodules upon chest HRCT, regardless of the presence of small cavities in the lungs (44, 45).

Sputum AFB smears and cultures were obtained by using standard methods (46). All clinical samples were cultured both on 3% Ogawa solid medium (Shinyang, Seoul, South Korea) and in liquid broth medium in mycobacterial growth indicator tubes (MGITs) (Becton-Dickinson and Co., Sparks, MD, USA).
During the study period, NTM species were identified by using a reverse blot hybridization assay of the \( \text{rpoB} \) gene (47), followed by multilocus sequencing analysis of the \( \text{rrs} \), \( \text{hpGSS} \), and \( \text{rpoB} \) genes (48). DST was performed by using the broth microdilution method (49). The MIC of CLR was determined on days 3 and 14 after incubation. Clinical isolates were considered susceptible (MIC of \( \leq 2 \mu g/ml \) at days 3 and 14), resistant (MIC of \( \geq 8 \mu g/ml \) at day 3), or inducibly resistant (susceptible at day 3 but resistant at day 14) to CLR (49). MICs for CFZ were not determined in this study period.

**Antibiotic therapy.** The initial treatment group was hospitalized for 4 weeks and received multiple antibiotics, including oral CFZ (100 mg/day) and a macrolide (AZM at 250 mg/day or CLR at 1,000 mg/day), along with an initial 4-week course of intravenous AMK (15 mg/kg of body weight/day) and cefoxitin (200 mg/kg/day; maximum of 12 g/day). Imipenem (750 mg three times per day) was substituted in the event of an adverse reaction to cefoxitin, such as leukopenia. After discharge, the oral regimen, including CFZ and a macrolide, was continued. If adverse effects to CFZ occurred, the dosage was reduced or discontinued. In the salvage treatment group, CFZ was added to the existing oral regimen in the outpatient setting or administered after rehospitalization for combination intravenous antibiotic treatment.

**Evaluation of treatment response.** Twelve months after the start of the CFZ-containing regimen, clinical, radiographic, and microbiological responses were evaluated. Symptomatic responses were determined by the attending physician. The physician’s subjective assessment of changes in respiratory condition was recorded 12 months after antibiotic treatment (50). Clinical responses were evaluated by retrospective medical record evaluation. Radiographic responses were evaluated by comparing the initial and follow-up HRCT images. When a follow-up HRCT image was not available, a chest radiograph was used instead. The radiographic images were reviewed by three of the authors (B.Y., S.M.M., and W.-J.K.), and a consensus was obtained for classifying the radiographic findings as “improved,” “unchanged,” or “worse.” Sputum examinations were performed at 3-month intervals during treatment. Sputum conversion was defined as three consecutive negative cultures, and the time of conversion was defined as the date of the first negative culture (8).

**Statistical analysis.** All data are presented as medians and IQRs for continuous variables and as numbers (percentages) for categorical variables. Data were compared by using the Mann-Whitney U test for continuous variables and the Pearson \( x^2 \) test or Fisher’s exact test for categorical variables. A two-sided \( P \) value of \( <0.05 \) was considered statistically significant for all analyses. All analyses were performed by using SPSS statistical software (SPSS version 23; IBM, Armonk, NY). Serial changes in AFB culture positivity were analyzed with generalized estimating equations using SAS version 9.4 (SAS Institute, Cary, NC).

**ACKNOWLEDGMENTS**

Charles L. Daley has received grants from Insmed Inc., not associated with this work. Otherwise, we have no conflicts of interest to declare.

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT, and Future Planning (NRF-2015R1A2A1A01003959) and by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (HI15C2778).

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June 2017 Volume 61 Issue 6 e20525-16 aac.asm.org 8

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