Nontuberculous Mycobacteria Pulmonary Disease

Subjects: Pathology

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Limited data are available regarding optimal treatment for refractory Mycobacterium avium complex-pulmonary disease (MAC-PD).We evaluated outcomes of inhaled amikacin (AMK) with clofazimine (CFZ) regimens as an add-on salvage therapy for refractory MAC-PD. We retrospectively analyzed 52 patients with refractory MAC-PD, characterized by persistently positive sputum cultures despite >6 months of treatment. Thirty-five (67%) patients had M. intracellulare-PD, and 17 (33%) patients had M. avium-PD. Twenty-seven (52%) patients received the salvage therapy for 12 months, whereas 25 (48%) patients were treated for <12 months due to adverse e ects or other reasons. Seventeen (33%) patients had culture conversion: 10 (10/27) in the 12-month treatment group and seven (7/25) in the <12-month treatment group (p = 0.488). Microbiological cure, defined as maintenance of culture negativity, was achieved in 12 (23%) patients; six (6/12) with accompanying symptomatic improvement were considered to have reached cure. Clinical cure, defined as symptomatic improvement with <3 consecutive negative cultures, was achieved in three (6%) patients. Overall, 15 (29%) patients achieved favorable outcomes, including microbiological cure, cure, and clinical cure. Inhaled AMK with CFZ may provide favorable outcomes in some patients with refractory MAC-PD. However, given the adverse e ects, more e ective strategies are needed to maintain these therapeutic regimens.

Keywords: Mycobacterium avium ; refractory ; inhalation ; amikacin ; clofazimine

1. Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous organisms that cause chronic disease, and the burdens of NTM-pulmonary disease (PD) are increasing worldwide[1][2][3]. A guideline of the American Thoracic Society/Infectious Disease Society of America recommended multidrug therapy for *Mycobacterium avium* complex (MAC)-PD consisting of a macrolide (i.e., clarithromycin or azithromycin), ethambutol, and rifamycin (i.e., rifampin or rifabutin) with or without addition of an injectable aminoglycoside[4][5]. The recent guidelines of the British Thoracic Society and Cystic Fibrosis Foundation/Society recommend regimens that include inhaled amikacin (AMK) or other oral agents[6][7]. In addition, data have recently been reported regarding inhaled AMK with clofazimine (CFZ) for the treatment of refractory NTM-PD[8][9]. Notably, the CONVERT trial showed the benefit of adding liposomal AMK inhalation for refractory MAC-PD[10]. In addition, synergistic effects of inhaled AMK and CFZ against NTM species have been observed in vitro[11]. Nevertheless, limited data are available regarding the efficacy of regimens that include inhaled AMK and CFZ in refractory MAC-PD.

2. Management

In this study, more than one-quarter (29%) of patients with refractory MAC-PD achieved a favorable outcome after initiation of inhaled AMK- and CFZ-containing regimens. Approximately one-third (33%) of patients had culture conversion, and microbiological cure occurred in 23% of patients. Our data suggest that regimens containing inhaled AMK with CFZ may yield favorable outcomes in some patients with refractory MAC-PD.

One of the most notable findings in our study was the high proportion of patients with strains that had pretreatment drug resistance. Approximately half (48%) of our patients had clarithromycin-resistant MAC strains at the initiation of the inhaled AMK and CFZ therapy. In previous studies of refractory MAC-PD, which showed culture conversion rates similar to our study, the proportions of patients with macrolide-resistant MAC strains were not high. In a study that included 23 patients with refractory MAC-PD who were treated with inhaled AMK therapy, 39% of patients had clarithromycin-resistant strains prior to treatment, and the conversion rate was 43%[12]. In a recent CONVERT study that evaluated the efficacy of AMK liposome inhalation suspension for patients with refractory MAC-PD, culture conversion was achieved by 29% of patients; however, only 22.9% of patients had pretreatment clarithromycin resistance[10]. Macrolides are the cornerstone of MAC-PD therapy, and development of macrolide resistance, mainly due to point mutations in the 23S rRNA gene, is

associated with poor treatment outcomes[13][14][15][16][17]. Thus, given that 36% (9/25) of our patients with clarithromycin-resistant strains experienced culture conversion, inhaled AMK- and CFZ-containing regimens may be worth consideration as treatment strategies, especially for patients with refractory MAC-PD.

AMK is one of the most important antibiotics for treatment of MAC-PD. Only 6.8%–10.4% of clinical strains of MAC are reportedly resistant to AMK[18], and a recent study indicated that use of aminoglycosides for ≥3 months was associated with treatment success in cavitary MAC-PD[19]. Inhaled AMK has been used to reduce adverse effects associated with long-term use of injectable AMK and to increase the therapeutic effect through lung absorption[20]. However, studies regarding the efficacy of inhaled AMK for refractory NTM-PD have shown varying culture conversion rates of 18%–67%[8][12][20][21]. These discrepancies may have been related to various epidemiological or clinical factors in the study cohorts. Notably, our patients had a long previous median treatment period of 28.5 months; 67% (35/52) of patients had cavitary lesions, which are known to be associated with poor response[22], and this high percentage of cavitary disease cases potentially contributed to the less-than-satisfactory treatment outcomes of many of our patients. Unfortunately, limited data are available regarding whether the differences in effectiveness of inhaled AMK depend on certain patient characteristics, such as the presence of cavitary lesions. Therefore, further studies are needed regarding the efficacy of inhaled AMK for refractory MAC-PD.

CFZ has a number of advantages for treatment of NTM-PD, including its long half-life, slow metabolic elimination, ability to achieve high concentrations in macrophages, and rapid localization within phagocytes. Laboratory studies have demonstrated synergistic effects of CFZ and AMK against NTM [15], and CFZ has been reported to be effective in treatment of MAC-PD[9][23][24]. However, unlike the laboratory findings, these clinical studies yielded inconsistent results. Moreover, appropriate criteria have not been established regarding an optimal MIC threshold of CFZ for MAC-PD, and further research is warranted on this issue.

In our study, approximately half (48%) of the patients discontinued regimens containing inhaled AMK and CFZ within 12 months, mostly due to adverse effects. Eventually, 33% (17/52) of patients discontinued the inhaled AMK, and 8% (4/52) of patients discontinued CFZ. The discontinuation rate of inhaled AMK tended to be higher in our study than in previous reports[8][12]. In a previous study, 27% (21/77) of patients with refractory NTM-PD discontinued inhaled AMK[8], and only 8% (2/26) of patients with refractory MAC-PD discontinued inhaled AMK in a Japanese study, despite the use of similar doses of AMK[12]. These differences were presumably because our patients had a high rate of previous usage of injectable aminoglycoside (58%) and long periods of previous aminoglycoside use (median, 7.0 months). Generally, CFZ is considered tolerable with no severe adverse effects. In our study, the rate of drug discontinuation due to CFZ side effects was not high, with only a few patients having troublesome adverse effects.

Notably, in our study, treatment for more than 12 months was not significantly associated with favorable outcome in multivariable analysis. This may have been due to the small numbers of patients included in the study. However, our data showed that negative culture conversion was achieved in some patients with treatment for less than 12 months. Further studies are required to confirm this point.

This study has several limitations. First, our data may not be generalizable to other geographic areas and clinical settings. Second, changes in symptoms were assessed using CAT scores, but there is little evidence that it is reasonable to use CAT scores to assess symptom changes in patients with NTM-PD. Third, treatment outcomes were reported based on combination therapy with a relatively short duration. Fourth, a recent study discussed the importance of the CFZ MIC level, but we did not measure the MIC levels of CFZ in this study[25]. Fifth, we included “clinical cure” in the definition of “favorable outcome” because patients who achieved “clinical cure” showed clinical and radiological improvement, and sputum samples could not be obtained in most cases with “clinical cure” due to decreased volume of sputum. However, it is possible that our data overestimated the efficacy of the treatment regimens. Finally, because 15 patients had NTM strains with intermediate resistance to AMK (MIC 32 μg/mL), the efficacy of our regimen containing inhaled AMK and CFZ may seem weak.

In conclusion, this is the first report of patients with refractory MAC-PD who were treated with inhaled AMK- and CFZ-containing regimens in a standard clinical setting. Our data showed that these regimens could provide favorable outcomes for some patients. However, given the adverse effects, a more effective strategy is needed to maintain these therapeutic regimens.

References

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