Effective treatment with macrolide and ethambutol for mycobacterium avium complex pulmonary disease

Masashi Ito, Yasuhiko Koga, Noriaki Sunaga, Toshitaka Maeno

Department of Respiratory Medicine, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan

Correspondence to: Yasuhiko Koga. Department of Respiratory Medicine, Gunma University Graduate School of Medicine, 3-39-15 Sho-wa machi Maebashi, Gunma 371-8511, Japan. Email: ykoga@gunma-u.ac.jp.

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We read with interest the article by Kim and colleagues regarding the importance of ethambutol in combination with macrolide for Mycobacterium avium complex (MAC) treatment (1). The authors compared the rates of culture conversion, microbiological cure, treatment failure, and recurrence in patients with MAC pulmonary disease (MAC-PD) following the maintenance of ethambutol and/or rifampicin with macrolide. Both the three-drug regimen (macrolide, ethambutol, and rifampicin) and two-drug regimen (macrolide and ethambutol) were associated with higher rates of microbiological cure, while another two-drug regimen (macrolide and rifampicin) was not. There was no significant difference between the three-drug regimen (macrolide, ethambutol, and rifampicin) group and the two-drug regimen (macrolide and ethambutol) group in culture conversion. Kim *et al.* described that maintenance therapy for MAC-PD with ethambutol was more strongly associated with the microbiological cure than that with rifampicin and the early cessation of ethambutol during the MAC-PD treatment due to uncertain adverse events should be avoided.

Although the combination of clarithromycin or azithromycin with ethambutol and rifampicin is a recommended option for MAC treatment, the optimal treatment regimen or period has not yet been established. Discontinuation of three standard drugs due to adverse events or avoidance of drug interaction is the most serious concern in the management of MAC, since treatment failure promotes the risk of macrolide resistance (MR). Therefore, we agree with the authors that a two-drug regimen, macrolide and ethambutol, is clinically important because it reduces treatment failure without affecting MR.

Previously, Miwa *et al.* reported that treatment with a two-drug regimen (clarithromycin and ethambutol) was superior to treatment with a standard three-drug regimen (clarithromycin, ethambutol, and rifampicin) for MAC-PD. The rates of sputum culture conversion were 40.6% and 55.0% with the three-drug regimen and the two-drug regimen, respectively. The incidence of adverse events leading to the discontinuation of treatment was 37.2% and 26.6% for the three-drug and two-drug regimens, respectively (2). Accounting for the efficacy of two-drug regimen in the literature, the mechanism of these results could be explained based on a decreased serum level of macrolide through the induction of cytochrome P-450 enzymes by rifampicin of a standard three-drug regimen (2). Although rifabutin, another rifamycin family member, induce less cytochrome P450 than rifampicin and it has been reported effective in the treatment of MAC-PD among patients with acquired immunodeficiency syndrome (3), the clinical issue of rifabutin is likely to be discontinued because of adverse events, uveitis.

Not only the effectiveness of the treatment outcomes but ethambutol has the possibility of reducing the risks of MR. Griffith *et al.* reported that macrolide combination therapy without ethambutol contributes to the acquisition of MR (4), and ethambutol is the next most important drug following macrolides for MAC-PD treatment. Therefore, discontinuation of ethambutol should be avoided for reducing the risks of MR. The major reason

for discontinuation of ethambutol is famous for ocular toxicity, we should effort to prevent emerging it. Griffith *et al*. reported that 8 of 139 patients (6%) on daily therapy of three-drug regimen (macrolide, ethambutol, and rifampicin) for MAC-PD were diagnosed with ethambutol ocular toxicity, but none of the 90 patients on intermittent therapy, which is a three-times-weekly regimen including macrolide, ethambutol, and rifampicin (5). In the evaluation of the clinical efficacy of intermittent therapy for nodular bronchiectatic MAC-PD, there was no significant difference between the daily and intermittent therapy groups in terms of clinical efficacy, such as sputum culture conversion. Additionally, ethambutol was more frequently discontinued in the daily group than in the intermittent group (n=24 *vs*. n=1, P<0.001) (5). Intermittent standard three-drug regimen is recommended to reduce the incidence of side effects in patients with non-cavitary nodular bronchiectatic MAC-PD (5,6). Intermittent therapy is not recommended for patients with cavitary MAC-PD. Recently, Moon *et al*. have reported that intermittent treatment of azithromycin and ethambutol for non-cavitary MAC-PD achieved a higher rate (76%) of sputum culture conversion after 12 months treatment (7). They suggested that intermittent azithromycin and ethambutol may be an optional treatment regimen for non-cavitary MAC-PD. A prospective randomized study is required to assess the efficacy and safety of the intermittent treatment of azithromycin and ethambutol for non-cavitary MAC-PD.

The risk of MR by a two-drug regimen without rifampicin is also considered an important issue. In the analysis of initial treatment of recurrent MAC-PD with MR, 29/90 (32.2%), 6/90 (6.7%), 23/90 (25.6%), and 5/90 (5.6%) patients received clarithromycin monotherapy, clarithromycin plus fluoroquinolone (FQ), clarithromycin plus rifampicin, and clarithromycin plus ethambutol, respectively (8). Using macrolide monotherapy or macrolide with only rifamycin or FQ was the major cause of MR development, but ethambutol did not result in the development of MR (4,8). The two-drug regimen (macrolide and ethambutol) is not associated with a significant risk of MR development. We need a prospective study to assess the efficacy and the risk of MR by a two-drug regimen, macrolide and ethambutol.

In the case of discontinuation of ethambutol, the optimal treatment regimen has not been established, and some combination therapy without ethambutol has been considered. Khadawardi *et al*. reported that the patients received a combination of macrolide-FQ-rifamycin without ethambutol didn't develop MR (9). FQ-containing therapy without ethambutol was conducted due to adverse events. Among patients who received macrolide-FQ-rifamycin without ethambutol, 3/9 patients had drug susceptibility testing >6 months after the starting of patients, and none developed MR (9). To assess the certain risks of MR and the treatment outcomes by a combination of macrolide-FQ-rifamycin, we need the study involving a large number of patients.

Amikacin injection is also considered beneficial in the treatment of MAC-PD, but the duration of treatment is limited due to the drug's side effects. Liposomal amikacin for the inhalational administration of amikacin is expected for refractory MAC-PD treatment. A prospective study is also desired to evaluate the efficacy of treatment with amikacin injection or inhalation.

For another treatment option for replacing rifampicin as the third drug in the standard three-drug regimen, clofazimine may also be prescribed instead of rifampicin. Treatment with macrolide, ethambutol, and clofazimine was successful in 20 of 30 patients (67%) with MAC-PD (10). A three-drug regimen with clofazimine instead of rifampicin showed better culture conversion (100%) than the standard three-drug regimen (71%) in a retrospective study of MAC-PD (11).

In conclusion, we agree with Kim and colleagues that a two-drug regimen, macrolide and ethambutol, is a better treatment option when we experience the discontinuation of rifamycin. A prospective study is required to assess the efficacy and risk of MR by the two-drug regimen. Ethambutol is a very important agent for the treatment of MAC-PD, we don't have any optimal treatment option without ethambutol. Therefore, we should effort to reduce the risks of ocular toxicity by administer the intermittent therapy to patients with non-cavitary MAC-PD.

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