Long-Term Combination Treatment of Azithromycin with Other Macrolides: A New Era

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Diffuse panbronchiolitis (DPB) is a chronic inflammatory disease of the airways. Before the discovery of low-dose erythromycin (EM) therapy in 1985, patients with DPB suffered from high rates of mortality despite treatment with a combination of various antibiotics and the use of supportive therapy such as oxygen administration (1). Low-dose erythromycin therapy (400 to 600 mg/day) was found to not only improve the survival of patients with DPB (2) through potential antimicrobial effects, but also it was suggested to possess anti-inflammatory properties (1). More recently, Kadota et al. have demonstrated that 6-month treatment with clarithromycin (CAM) is also safe and effective at improving clinical conditions of patients with DPB, while also providing anti-inflammatory effects (3). Most recently, the previously mentioned 14-membered macrolides (EM and CAM), as well as 15-membered macrolide, azithromycin (AZM) were found to elicit immunomodulatory effects that are not demonstrated by 16-membered macrolides (4). Since AZM has been used as a three-day regimen or one-day (extended-release formula) in Japan, it is rarely used as a long-term treatment for respiratory infections.

In this issue, Yamamoto et al. report a case of refractory chronic respiratory tract infection due to *Pseudomonas aeruginosa* that was successfully controlled by combination therapy using CAM (400 mg once daily) and AZM (250 mg once daily) treatment for 2 years (5). In 2011, two review articles concerning long-term treatment of AZM were published regarding patients with cystic fibrosis (CF) (6, 7). It has been demonstrated that long-term use of AZM can improve lung function, especially for *Pseudomonas aeruginosa*-colonized CF patients with no evidence of increased adverse events with AZM use (6-14). In addition, Li et al. have recently reported that long-term treatment of AZM is effective for controlling DPB in Chinese patients (Table 1) (15). Furthermore, it has also been reported that

long-term treatment of AZM is effective for preventing exacerbation of chronic obstructive pulmonary diseases (COPD) (Table 1) (16-18).

Yamamoto et al. examined the differences in the effects of CAM and AZM, and discovered that AZM and CAM exerted different immunomodulatory effects in murine dendritic cells (5, 19). AZM increased interleukin (IL)-10 production and inhibited the excess immune response, whereas CAM inhibited IL-2 and IL-6 production. Although both drugs (AZM and CAM) affected immune responses, they exhibited different immune alterations. It was suggested that these differences in immunomodulatory effects explain the improved efficacy of the combination therapy of CAM and AZM in comparison to treatment with one drug alone (5).

Although the clinical efficacy of long-term treatment of azithromycin has been well established overseas, clinical application in Japan is lacking. Therefore, long-term treatment of azithromycin or long-term combination treatment of azithromycin with other macrolides should be considered if other macrolides are not effective. Additionally, the efficacy of macrolide combination therapy should be further examined in clinical studies as well as in laboratory studies.

Author's disclosure of potential Conflicts of Interest (COI).

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Table 1. Main Characteristics of the Long-term Azithromycin Treatment

Study	Disease	Patient age (years)	Screened patients (N)	Pathogen	Dose of azithromycin	Length of treatment	Efficacy	Adverse events
Equi <i>et al.</i> (2002) ⁸	Cystic fibrosis	8–18	41	PA or non-PA	250 mg (≤ 40 kg) or 500 mg (> 40 kg), per day	3 months	Increase in FEV1 Improved QOL. Reduced CRP levels, respiratory exacerbations, and lung function decline rate	None reported Urticarial reaction in a patient
Wolter <i>et al.</i> (2002) ⁹	Cystic fibrosis	≥ 18	60	PA or non-PA	250 mg, per day	3 months		
Saiman <i>et al.</i> (2003) ¹⁰	Cystic fibrosis	≥ 6	251	PA	250 mg (< 40 kg) or 500 mg (≥ 40 kg), 3 times per week	168 days	Increase in FEV, less exacerbation risk, and weight gain	Nausea (17%), diarrhea (15%), and wheezing (13%) Duodenal bleeding in one patient
Rotschild <i>et al.</i> (2005) ¹¹	Cystic fibrosis	6–36.7	18	PA or non-PA	250 mg twice weekly	3 months	Not effective	
Clement <i>et al.</i> (2006) ¹²	Cystic fibrosis	6–21	82	PA or non-PA	250 mg (≤ 40 kg) or 500 mg (> 40 kg), three times per week	12 months	Decrease in exacerbations and antibiotic use	None reported
Steinkamp <i>et al.</i> (2008) ¹³	Cystic fibrosis	≥ 8	40	PA	500 mg (20–29 kg), 750 mg (30–39 kg), 1000 mg (40–49 kg), or 1250 mg (50 kg), once per week	8 weeks	Ameliorated inflammatory reactions and QOL	None reported
Saiman <i>et al.</i> (2010) ¹⁴	Cystic fibrosis	6–18	324	uninfected with PA	250 mg (18–35.9 kg) or 500 mg (≥ 36 kg), 3 days per week	168 days	Not effective	None reported
Li <i>et al.</i> (2010) ¹⁵	Diffuse panbronchiolitis	10–80	51	PA or non-PA	500 mg, per day intravenously first 1–2 weeks, then 500 mg, per day, orally for 3 months, then 3 times per week	totally 6 to 12 months	Elimination of symptoms	None reported
Blasi <i>et al.</i> (2010) ¹⁶	COPD and tracheostomy	72 ± 7 (mean $\pm$ SD)	11	PA or non-PA	500 mg, three times per week	6 months	Reduced exacerbations, hospitalizations, and improved QOL	None reported
Albert <i>et al.</i> (2011) ¹⁷	Exacerbation of COPD	65 ± 9 (mean $\pm$ SD)	570	PA or non-PA	250 mg, per day	12 months	Decrease in exacerbations and improved QOL	Hearing decrements in a small percentage of subjects
Pomares <i>et al.</i> (2011) ¹⁸	Severe COPD and repeated exacerbations	70.9 ± 7.4 (mean $\pm$ SD)	20	PA or non-PA	500 mg, three times per week	12 months	Reduced acute exacerbations	None reported
Yanamoto <i>et al.</i> (2012) ⁵	Bronchiectases	60 (1 female)	1	PA	250 mg, per day	24 months	Effective only in combination with clarithromycin	None reported

COPD, chronic obstructive pulmonary disease; PA, *P. aeruginosa*; non-PA, pathogenic bacteria other than *P. aeruginosa*.

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