Review Article

Macrolide antibiotics: 25 years of use and the future treatment of common diseases

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ABSTRACT

The novel mechanism of action of macrolides was discovered when a significant improvement in the survival of patients with diffuse panbronchiolitis (DPB) receiving low dose of erythromycin was observed, and when their beneficial effect was found to be independent of their anti-microbial activity. Macrolides that are members of the 14- and 15-ring groups show beneficial effects against DPB but not those of the 16-ring groups. We could recognize these effects of macrolides because their administration was associated with reduced inflammatory response in chronic airway diseases including upper- and lower-respiratory tract infections. The anti-inflammatory action of macrolides during infections by bacteria and virus with high virulence has been recently the focus of several studies. Thus, this interesting anti-inflammatory effect of macrolide is currently being assessed not only in the rare condition of DPB but also in common diseases such as viral airway infection. In this review, we will summarize the use of macrolides in common and rare diseases during the past 25 years.

Key words: Common diseases, diffuse panbronchiolitis, macrolide antibiotics, treatment

BACKGROUND

Macrolide antibiotics (MAs) can significantly improve the prognosis of diffuse panbronchiolitis (DPB). MAs are also effective in the treatment of chronic paranasal sinusitis and pyocyanic infections, which indicates that MAs offer anti-inflammatory effects in addition to antibacterial effects. The anti-inflammatory effects are important not only to the host, but also to the pathogen itself. In recent years, MAs have also been shown to be effective in the treatment of some common diseases, including chronic obstructive pulmonary disease (COPD) and influenza virus infections. In these cases, MAs slow disease progression and reduce disease severity. This article summarizes 25 years of MA use in DPB and introduces the concept of the use of MAs for common diseases.

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Improved survival rate of patients with diffuse panbronchiolitis

Many common diseases result in chronic respiratory tract infections, including chronic obstructive pulmonary disease (COPD) and bronchiectasis. Other rare diseases can also lead to chronic respiratory tract infections, including cystic fibrosis (CF), Yellow-nail syndrome, Young's syndrome, common variable immunodeficiency (CVID), and bronchopulmonary sequestration (BLS). These diseases usually occur simultaneously with paranasal sinusitis and, clinically, the combination of chronic bronchitis and paranasal sinusitis is called sinobronchial syndrome (SBS). Diffuse panbronchiolitis (DPB) is a specific type of SBS, which is a chronic inflammatory disease of the airway involved with the respiratory bronchioles of both lungs.[1,2] DPB was first reported by Homma and Yamanaka in 1969.[3] As its name implies, the inflammatory lesions are diffusely

distributed and affect all layers of the respiratory bronchiole wall. The main clinical manifestations of DPB include persistent cough, expectoration, and dyspnea on exertion with chronic parasinusitis or past history of the condition, and nodular shadows in a diffuse distribution in both lungs seen on a chest radiograph or centrilobular nodular shadows in both lungs seen on the chest CT.[4] Other clinical manifestations include intermittent coarse crackles on both chest auscultation, a ratio of the forced expiratory volume, and forced vital capacity in 1 s (FEV_1/FVC) lower than 70% and a partial pressure of oxygen in arterial blood (PaO_2) less than 80 mmHg (1 mmHg = 0.133 kPa), and a serum potency of greater than or equal to 1:64 in a cold agglutinin titer.[5,6] On autopsy of a patient with DPB, many small, off-white nodes will be distributed on the surface of the lung, which, if touched, feel rough like small sand particles. Evaluation of a cross-section of the lungs may reveal many nodes centered on the bronchiole and, sometimes, bronchiectasis subsequently appears.[7] Several pathological features identify DPB. First, bronchiolitis appears on respiratory bronchioles, while other lung areas appear normal. Second, DPB is characterized by transmural inflammation of the bronchioles, while the alveolar wall is generally uninvolved. Third, the inflammation of the bronchioles and respiratory bronchioles will cause narrowing and blockage in the bronchioles. Foam cells can be seen on the alveolus septum and mesenchyme. Manifestations of bronchiole and respiratory bronchiole inflammation include thickening of the vessel wall and the infiltration of lymphocytes, plasmocytes, and histiocytes.[8] Prior to 1980, DPB therapy primarily included glucocorticoids, antibiotics, expectorants, and bronchodilators, but the clinical efficacy of such treatment was not satisfactory.[9] In 1982, Professor Kudoh unexpectedly found a patient with DPB whose symptoms and chest radiograph findings improved after therapy with erythromycin (EM; 600 mg/d) for 2 years. In 1984, a report was published in Japan confirming that long-term therapy with EM could significantly improve the prognosis of four patients with DPB. Kudoh *et al*.[10] investigated the treatment of 500 DPB patients and found that the survival rate of DPB patients who received long-term therapy with low-dose EM was significantly higher than that of patients treated with other common antibiotics and antipseudomonas antibiotics. Also, the efficacy of EM therapy (600 mg/d), measured by six indices (dyspnea, chest radiograph, PaO_2, FEV_1, C-reactive protein, and amount of expectoration), was superior to placebo. The symptoms of chronic paranasal sinusitis also improved with long-term, low-dose EM treatment for DPB. For 26 patients with chronic paranasal sinusitis who experienced no symptom improvement after operation, all symptoms improved after taking EM 400-600 mg/d for 7-9 months. Forty-five patients with drug-resistant chronic paranasal sinusitis were treated with clarithromycin (CAM, 400 mg/d) for 8-12 weeks. Overall, 73.3% of the patients experienced symptom improvement, and patients who received the therapy for 12 weeks also improved and experienced no obvious side effects. Hashiba recommended that CAM and roxithromycin can be used for the treatment of chronic paranasal sinusitis, but of these had almost no bactericidal effect.[11] The recommended adult doses of MAs are as follows: EM 400-600 mg/d, CAM 200 mg/d, and roxithromycin 150 mg/d. For children, EM 10 mg/kg and CAM 5 mg/kg were the recommended doses.

Some researchers have reported that long-term treatment with azithromycin, an MA with a 15-membered ring structure, could improve the lung functions of CF patients.[12] A randomized, controlled trial of CF patients with *Pseudomonas aeruginosa* infection proved that MAs, especially azithromycin, had positive effects on CF.[13] As of October 2007, there were 87 reports of the positive efficacy of MAs on the treatment of CF in the Lancet. Interest in the clinical application of MAs is gradually increasing. The international community has recognized MAs as the standard therapy for DPB.

Mechanism of action for MAs

Although MAs therapy has been established in the clinical treatment of DPB, the detailed pharmacological mechanism remains unclear. Clinically, the usual dose of EM is not appropriate against *P aeruginosa*. However, long-term treatment with low-dose EM has shown significant efficacy in DPB patients with a simultaneous *P aeruginosa* infection. The effective time of MA therapy is approximately 2 months, which contradicts the mechanism of action for an antibacterial agent. To clarify the use and application of MAs, a group was established in Japan in 1994 to study MAs. The group is composed of physicians from Respiratory and Otolaryngology Departments and basic research personnel and it continuously reports the knowledge and research progress relating to MAs.

The mechanism of action of MAs has been described from several aspects. First, MAs decrease the mucus secretion of the airways.[14] Airway mucus is primarily composed of the product secreted by the goblet epithelial cells and the submucosal glands and the tissue transudate. The viscoelasticity of the mucus is determined by the mucoprotein (MUC) secreted cooperatively by the goblet cells and submucosal glands. In 1995, Tamaoki reported that after 8 weeks of therapy for chronic respiratory tract infections with low-dose CAM (100 mg twice daily by mouth), the sputum excretion volume decreased from 130 to 60 g/d ($P < 0.01$).[15] Other studies also reported that EM blocked the chloride channel in epithelial cells of the respiratory tract and then decreased water secretion into the tracheal cavity, resulting in a decreased sputum volume. MUC 5AC exists in the epithelial goblet cells of the human trachea. As demonstrated by the *in-situ* hybridization method and nucleic acid hybridization technologies, MAs can decrease the expression of the MUC 5AC gene. Further,

lipopolysaccharides (LPS) can increase the gene and protein expressions of MUC 5AC, but EM and CAM can inhibit the LPS-induced MUC 5AC gene expression. Therefore, MAs can influence gene expression on the transcriptional level. Second, MAs influence inflammatory cells and inflammatory mediators. Some researchers observed that the neutrophilic granulocyte percentage of DPB patients was significantly higher than healthy volunteers ($P < 0.01$). However, after EM treatment, the neutrophilic granulocyte percentage decreased significantly ($P < 0.01$) and the reactivity of the neutrophilic granulocyte to chemical factors also decreased ($P < 0.01$).[16] Researchers indicated that after treatment of DPB patients with EM (600 mg/d) for 3 months, the number of neutrophilic granulocytes, the interleukin (IL)-8 concentration, and the protease concentration of neutrophilic granulocytes all decreased compared to before treatment ($P < 0.05$).[17]

There are five primary hypotheses regarding the mechanism of action for MAs on host defense:

1. EM decreases the secretion of IL-8 from airway epithelial cell;
2. MAs inhibit the release of leukotriene B4 (LT-B4) and elastase from neutrophilic granulocytes and decrease the accumulation of neutrophilic granulocytes on the airway mucous membrane;
3. MAs inhibit the generation of the intercellular cell adhesion molecule (ICAM-1) and the vascular cell adhesion molecule (VCAM);
4. MAs decrease the secretion of mucin from the airway epidermis and block the chloride channel to inhibit the secretion of water, which reduces subsequent mucous secretion in the airway; and
5. MAs inhibit the generation of peroxidase and defensins to reduce tissue injuries.

The effects of MAs on bacteria

For *P aeruginosa*, the quorum sensing (QS) system influences the generation and expression of the main virulent factor of bacteria and plays an important role in the coordination of bacterial activity and the regulation of virulent gene expression. *P aeruginosa* has two molecules involving QS systems, las and rhl, in which 3-oxododecanoyl-C12-homoserine lactone (3-oxo-C12-HSL) and C4-homoserine lactone (C4-HSL) are the auto-inducers. Both auto-inducers can be detected in the sputum of patients with chronic *P aeruginosa* infections.[18] Exposure to different antibiotics for 48 h influences the viability of *P aeruginosa*. Specifically, azithromycin, EM, and CAM exhibit dose-dependent bactericidal activity and 0.5 μg/mL azithromycin, 8 μg/mL EM, and 4 μg/mL CAM can reduce the viability of the bacteria by 10%. However, josamycin and oleandomycin have no bactericidal activity with concentrations as high as 64 μg/mL.[19] MAs control the *P aeruginosa* infection and alter the host immune response by decreasing the concentration of auto-inducers in the QS system. Tateda *et al*.[20] found that 2 μg/mL azithromycin significantly decreased the transcription of lasI by 80% and rhlI by 50% to reduce the generation of 3-oxo-C12-HSL and C4-HSL compared with the control group. EM, CAM, and roxithromycin can decrease the expression of the lasI gene, but oleandomycin and josamycin cannot.

The creation of a biofilm is a survival strategy adopted by bacteria to avoid host immune offence and the damaging effects of antibiotics. MAs decrease the formation of biofilms and reduce the drug resistance of *P aeruginosa* to other antibiotics.[21] An MA can help other antibiotics penetrate the body to enhance its bactericidal effects. Feasibility research is being conducted to investigate if MA, while offering no antibacterial effect when used as a single drug, will reduce the minimal inhibitory concentration of other antibiotics. MLs can exhibit enhancement of bactericidal effect of other anti-microbial agents.

Effects of MAs on transcription factor

MAs restrain the host factor with over-expression. The cell cycle stage in which inhibitory action occurs is a focus of current research. Nuclear transcription factor-κB (NF-κB) is the regulating and controlling factor on the upper stream of IL-8 and confers the chemotaxis function of neutrophilic granulocytes. EM can inhibit the activation of NF-κB in cell nuclei to reduce transcription and promote anti-inflammatory action. *In-situ* hybridization technology has been applied to lung biopsy specimens of DPB patients to prove that IL-8 mRNA is detected in alveolar macrophages, epithelial cells, and endothelial cells, which indicates that IL-8 is an important chemotactic factor in airway inflammation. Takizawa *et al*. reported that EM and CAM reduce the IL-8 mRNA level in epithelial cells in the bronchus of human beings; but ampicillin, cefazolin, achromycin, and josamycin do not offer the same action.[22] Desaki *et al*. have applied nucleic acid hybridization to demonstrate that EM reduces the expression of IL-8 mRNA.[23] The application of electrophoretic mobility shift assay shows that EM can reduce the expression of NF-κB and reactive protein-1 (AP-1), the two primary regulatory factors of IL-8 gene transcription, in a time-dependent manner. NF-κB initially exists in cytoplasm and must be activated and shifted to karyon before exerting its action. Both TNF-α and IL-1 participate in its activation and EM inhibits the activation of NF-κB by reducing the secretion of TNF-α and IL-1.

Effects of MAs on viruses

In April 2009, the outbreak of Influenza A virus H1N1 induced global panic. The toxicity of the seasonal influenza virus was not strong, but since the human body has no immunity to mutant viruses, the infection rate was high. The influenza virus cannot reproduce by itself and it needs to infect the epidermal cells of human beings or other animals such as pigs or birds to replicate and proliferate. The frequency of infections of seasonal influenza in youth is

high, and the fatality rate associated with seasonal influenza infections in the elderly is high. The high fatality rate in the elderly may be related to the weakness of epithelial cells against oxidative stress and subsequently occurring secondary bacterial infection caused by damage to the epithelial cells; MAs can reduce the damage to the cilia of epithelial cells by the virus to avoid the secondary infection caused by bacteria, which could increase the survival rate among older patients.

CAM can inhibit the duplication of some influenza viruses. In concentrations of 12.5 and 25 μg/mL, CAM can reduce the duplication of H1N1 influenza virus, but has no significant effect on the duplication of the H3N2 influenza virus. CAM acts at the middle and late stages of virus replication to reduce the duplication of progeny virus in the infected cell.[24] In the early stage of virus infection (2-3 d), the secretion of IL-12 is increased to promote the production of interferon (IFN)-γ and immunoglobulin (Ig) A on the mucous membrane of the respiratory tract in order to enhance the immunity of the mucous membrane.[25] During the middle and late stages (after 6d) of a deadly influenza infection model, excess IFN-γ is produced. The clinical significance of reducing this immune reaction and its ability to affect the fatality rate are currently being investigated and are expected to be future targets of MA therapy.

The influenza vaccine is the first choice for preventing the flu. Some researchers have indicated that the combination of anti-viral drugs and MAs could improve the effect of the vaccine. That is, the use of MAs to treat a viral infection can mitigate the clinical symptoms associated with an infection and reduce the incidence of severe infections. Epidemiological surveillance reveled those mechanistic hypothesis of MLs on influenza infection.[26]

Therefore, it is recommended that MA therapy be used to treat an influenza infection in older individuals who suffer from chronic respiratory or cardiovascular diseases.

Effects of MAs on COPD

The efficacy of long-term, low-dose MAs for rare diseases has received extensive attention. The effects of MAs for common diseases have also become a focus of current research. The use of MAs has been expanded from the treatment of DPB to that of COPD, bronchiectasis, bronchial asthma, chronic paranasal sinusitis, and exudative otitis media. The number of MAs available has also increased from the original EM to include CAM, roxithromycin, and azithromycin. The clinical application of MA treatment for chronic inflammatory diseases has been gradually recognized by European & American countries. The following example demonstrates the current research process with COPD.

COPD is a chronic inflammatory disease of the respiratory tract and it is most commonly caused by smoking. COPD causes damage to the airway and alveolar wall due to chronic inflammation, indicated by a high proportion of neutrophilic granulocytes, which causes repeated acute exacerbations. Most practitioners believe that the acute exacerbations of COPD mostly involve infections with rhinovirus. MA treatment can reduce the adhesion of rhinovirus to the respiratory tract and mitigate the acute exacerbations in COPD patients. Several clinical trials at many centers have reached the same conclusion.[27] A prospective clinical trial by Seemungal *et al.*[28] also demonstrated that MAs could reduce the frequency of acute exacerbation of COPD and shorten the course of the exacerbation. An *in vitro* study showed that cigarettes could damage the epithelial cells of the alveoli, but CAM could mitigate the damage to smokers' alveoli by reducing the number of neutrophilic granulocytes, macrophages, and T lymphocytes. Researchers also indicated that CAM could prevent emphysema caused by smoking.[29] EM has significant efficacy in emphysema with no obvious expectoration. The effects of MAs on chronic alveolar damage in emphysema need to be examined by future research. Large-scale controlled trial using AZM also improved survival of COPD by reducing the acute exacerbation.[30]

SUMMARY

Since McGuire's discovery of EM, an MA with a 14-membered ring structure, in 1952, treatment with MAs for gram positive cocci, legionella and mycoplasma pneumonia, and nontuberculous acid-fast bacillus has been well established. MAs can also stimulate the digestive system. In recent years, new MAs with a mechanism of promoting peristalsis of the intestinal canal have been under development and are gradually being applied to therapies for digestive system diseases. MAs offer anti-inflammatory action and their use extends from research of rare diseases to treatment of common diseases, such as influenza and COPD. The international community is awaiting a new MA with anti-inflammatory effects, but without antibacterial effects.

REFERENCES

1. Homma H, Yamanaka A, Tanimoto S, Tamura M, Chijimatsu Y, Kira S, *et al*. Diffuse panbronchiolitis: A disease of the transitional zone of the lung. Chest 1983;83:63-9.
2. Corne J. Diffuse panbronchiolitis: A new Japanese export? Lancet 1996;348:1465-6.
3. Yamanaka A, Saiki S, Tamura S, Saito K. Problems in chronic obstructive bronchial diseases, with special reference to diffuse panbronchiolitis. Naika 1969;23:442-51.
4. Isihara K, Iwasaki H, Katagami N, Sakamoto H, Lee E, Umeda B, *et al*. Characteristics in airwa resistance and uneven ventilation in patients with diffuse panbronchiolitis (DPB) and diffuse pulmonary emphysema. Kokyu Junkan 1984;32:627-32.
5. Nakata K. Revision of clinical guidelines for diffuse panbronchiolitis. In: Annual Report on the Study of Diffuse Lung Disease in 1998. Grant in Aid from the Ministry of Health and Welfare of Japan. Tokyo, 1999:109-111 (in Japanese).
6. Poletti V, Casoni G, Chilosi M, Zompatori M. Diffuse panbronchiolitis. Eur Respir J 2006;28:862-71.

7. Maeda M, Saiki S, Yamanaka A. Serial section analysis of the lesions in diffuse panbronchiolitis. Acta Pathol Jpn 1987;37:693-704.
8. Iwata M, Colby TV, Kitaichi M. Diffuse panbronchiolitis: Diagnosis and distinction from various pulmonary diseases with centrilobular interstitial foam cell accumulations. Hum Pathol 1994;25:357-63.
9. Takizawa H, Tadokoro K, Miyoshi Y, Horiuchi T, Ohta K, Shoji S, *et al*. Serological characterization of cold agglutinin in patients with diffuse panbronchiolitis. Nihon Kyobu Shikkan Gakkai Zasshi 1986;24:257-63.
10. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. Am J Respir Crit Care Med 1998;157: 1829-32.
11. Hashiba M, Kondo K, Hamashima A, Koseki A, Miyamoto N, Murakami S, *et al*. Effect of macrolide therapy on microbes in nasal cavity and larynx of patients with chronic paranasal sinusitis. Jpn J Antibiot 2001;54 Suppl C:102-5.
12. Jaffe A, Francis J, Rosenthal M, Bush A. Long-term azithromycin may improve lung function in children with cystic fibrosis. Lancet 1998;351:420.
13. Saian L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, *et al*. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: A randomized controlled trial. JAMA 2003;290:1749-56.
14. Goswami, SK, Kivity S, Marom Z. Erythromycin inhibits respiratory glycoconjugate secretion from human airways in vitro. Am Rev Respir Dis 1990;141:72-8.
15. Tamaoki J, Takeyama K, Tagaya E, Konno K. Effect of clarithromycin on production and its rheological properties in chronic respiratory tract infections. Antimicrob Agents Chemother 1995; 39:1688-90.
16. Kadota J, Sakito O, Kohno S, Sawa H, Mukae H, Oda H, *et al*. A mechanism of erythromycin treatment in patients with diffuse panbronchiolitis. Am Rev Respir dis 1993;147:153-9.
17. Oishi K, Sonoda F, Kobayashi S, Iwagaki A, Nagatake T, Matsushima K, *et al*. Role of interleukin-8 (IL-8) and an inhibitory effect of erythromycin on IL-8 release in the airways of patients with chronic airway diseases. Infect Immun 1994;62:4145-52.
18. Tateda K, Standiford TJ, Pechere JC, Yamaguchi K. Regulatory effects of macrolides on bacterial virulence: Potential role as quorum-sensing inhibitors. Curr Pharm Des 2004;10:3055-65.
19. Tateda K, Ishii Y, Matsumoto T, Furuya N, Nagashima M, Matsunaga T, *et al*. Direct evidence for antipseudomonal activity of macrolides: Exposure-dependent bactericidal activity and inhibition of protein synthesis by erythromycin, clarithromycin, and azithromycin. Antimicrob Agents Chemother 1996;40:2271-75.
20. Tateda K, Comte R, Pechere JC, Köhler T, Yamaguchi K, Van Delden C. Azithromycin inhibits quorum sensing in Pseudomonas aeruginosa. Antimicrob Agents Chemother 2001;45:1930-3.
21. Hoffmann N, Lee B, Hentzer M, Rasmussen TB, Song Z, Johansen HK, *et al*. Azithromycin blocks quorum sensing and alginate polymer formation and increases the sensitivity to serum and stationary-growth-phase killing of Pseudomonas aeruginosa and attenuates chronic P. aeruginosa lung infection in Cfftr(-/-) mice. Antimicrob Agents Chemother 2007;51:3677-87.
22. Takizawa H, Desaki M, Ohtoshi T, Kawasaki S, Kohyama T, Sato M, *et al*. Erythromycin modulates IL-8 expression in normal and inflamed human bronchial epithelial cells. Am J Respir Crit Care Med 1997;156:266-71.
23. Desaki M, Takizawa H, Ohtoshi T, Kasama T, Kobayashi K, Sunazuka T, *et al*. Erythromycin suppresses nuclear factor-kappaB and activator protein-1 activation in human bronchial epithelial cells. Biochem Biophys Res Commun 2000;267:124-8.
24. Miyamoto D, Hasegawa S, Sriwilaijaroen N, Yingsakmongkon S, Hiramatsu H, Takahashi T, *et al*. Clarithromycin inhibits progeny virus production from human influenza virus-infected host cells. Biol Pharm Bull 2008;31:217-22.
25. Tsurita M, Kurokawa M, Imakita M, Fukuda Y, Watanabe Y, Shiraki K. Early augmentation of interleukin (IL-12) level in the airway of mice administered orally with clarithromycin or intranasally with IL-12 results in alleviation of influenza infection. J Pharmacol Exp Ther 2001;298:362-8.
26. Azuma A, Yamaya M, Kadota J, et al. The use of macrolides in the 2009 H1N1 virus infection outbreak: A survey of general practice in Japan. Respir Invest 2013;51:257-9.
27. Yamaya M, Azuma A, Tanaka H, Takizawa H, Chida K, Taguchi Y, *et al*. Inhibitory effects of macrolide antibiotics on the exacerbations and hospitalization in chronic obstructive pulmonary disease in Japan: A retrospective multicenter analysis. J Am Geriatr Soc 2008;56:1358-60.
28. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med 2008;178:1139-47.
29. Nakanishi Y, Kobayashi D, Asano Y, Sakurai T, Kashimura M, Okuyama S, *et al*. Clarithromycin prevents smoke-induced emphysema in mice. Am J Respir Crit Care Med 2009;179:271-8.
30. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, *et al*. COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.

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