Auris Nasus Larynx xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Past, present and future of macrolide therapy for chronic rhinosinusitis in Japan

Takeshi Shimizu [a,*], Harumi Suzaki [b]

[a] Department of Otorhinolaryngology, Shiga University of Medical Science, Otsu, Japan
[b] Nasal and Paranasal Sinus Disease and Allergy Institute, Tokyo General Hospital, Tokyo, Japan

ARTICLE INFO

Article history:
Received 27 July 2015
Accepted 26 August 2015
Available online xxx

Keywords:
Chronic rhinosinusitis
Macrolide therapy
Nasal polyp
Erythromycin
Clarithromycin
Azithromycin

ABSTRACT

In 1984, the effectiveness of low-dose, long-term erythromycin treatment (macrolide therapy) for diffuse panbronchiolitis (DPB) was first reported in Japan. The 5-year survival rate for DPB improved from 62.9 to 91.4% after implementation of macrolide therapy. The usefulness of this treatment has since been demonstrated in patients with other chronic airway diseases, such as chronic bronchitis, cystic fibrosis, bronchiectasis, bronchial asthma, and chronic rhinosinusitis (CRS). The new 14-membered macrolides clarithromycin and roxithromycin and the 15-membered macrolide azithromycin are also effective for treating these inflammatory diseases. The mechanism of action of the 14- and 15-membered macrolides may involve anti-inflammatory rather than anti-bacterial activities. Macrolide therapy is now widely used for the treatment of CRS in Japan; it is particularly effective for treating neutrophil-associated CRS and is useful for suppressing mucus hypersecretion. However, macrolide therapy is not effective for eosinophil-predominant CRS, which is characterized by serum and tissue eosinophilia, high serum IgE levels, multiple polyposis, and bronchial asthma. Recent reports have described the clinical efficacy of macrolides in treating other inflammatory diseases and new biological activities (e.g., anti-viral). New macrolide derivatives exhibiting anti-inflammatory but not anti-bacterial activity thus have therapeutic potential as immunomodulatory drugs. The history, current state, and future perspectives of macrolide therapy for treating CRS in Japan will be discussed in this review.

1. History of macrolide therapy

In April of 1882, a patient with diffuse panbronchiolitis (DPB) suddenly called upon Prof. Shoji Kudoh at the Nippon Medical University Hospital after an interval of 2 years and said, "I am recovered." DPB is an intractable chronic airway disease with a poor prognosis (the 5-year survival rate in 1970–1979 was 62.9% in Japan) and is characterized by chronic recurrent bronchiolitis and peribronchiolitis with infiltration of lymphocytes and plasma cells. HLA B54 is a frequent halotype, and DPB primarily affects East Asian people. Prof. Kudoh examined the patient and surprisingly found that he had indeed recovered. Prof. Kudoh asked what kind of treatment the patient had been given, and the patient reported that he had been treated with low-dose (600 mg/day) erythromycin (EM) for 2 years by a general practitioner. Upon treating his DBP patients with low-dose EM, Prof. Kudoh found that this treatment was very effective. In 1984, he first reported the clinical effectiveness of low-dose, long-term EM treatment (macrolide therapy) in 18 DPB patients. The clinical efficacy of macrolide therapy in treating DPB in Japanese patients was later confirmed, as the 5-year survival rate for DPB improved to 91.4% after macrolide therapy became widespread (1985–1990) [1].

Although EM's mechanism of action was initially unclear, some researchers suggested that it involves anti-inflammatory rather than anti-bacterial activity because (1) treatment with a low dose (i.e., one-half of the usual dose) demonstrated a good response, (2) long-term (1–3 months) treatment was required, and (3) the treatment was also effective against EM-resistant bacteria such as *Pseudomonas aeruginosa*. Later, many investigators demonstrated that 14- and 15-membered macrolides exhibit various anti-inflammatory and immunomodulatory activities [2], including the inhibition of mucus hypersecretion [3] and ion transport [4]; activation of mucociliary function [5]; modulation of cytokine/chemokine production [6]; suppression of transcription factor and inflammatory cytokine gene expression [7]; immunomodulatory effects on inflammatory cells, fibroblasts, and epithelial cells

* Corresponding author at: Department of Otorhinolaryngology, Shiga University of Medical Science, Seta-Tsukinowa, Otsu, Shiga 520-2192, Japan. Tel.: +81 77 548 2261; fax: +81 77 548 2783.
E-mail address: shimizu@belle.shiga-med.ac.jp (T. Shimizu).

http://dx.doi.org/10.1016/j.anl.2015.08.014
0385-8146/

[8–10]; and inhibition of bacterial functions such as quorum-sensing and biofilm formation [11,12].

DPB is a subtype of sinobronchial syndrome and is often associated with intractable chronic rhinosinusitis (CRS). In 1990, Suzaki et al. [13] examined the effects of low-dose, long-term EM treatment on the accompanying CRS symptoms in DPB patients and found that this treatment was also effective for concomitant CRS. In 1991, Suzaki's group [14] first reported the clinical efficacy of low-dose, long-term EM treatment (400–600 mg/day for 3–19 months) in a study of 26 CRS patients without DPB. The effectiveness of EM (400–600 mg/day for adults and 200–300 mg/day for children, for 3–27 months) in treating intractable CRS was reported in 1992 from a study of 130 patients (4–78 years old, mean 43 years) [15]. The clinical benefits of low-dose, long-term EM treatment (macrolide therapy) for other chronic airway diseases has also been demonstrated, such that macrolide therapy is now used to treat CRS [16,17], chronic bronchitis [18,19], cystic fibrosis [20], bronchiectasis [21], and bronchial asthma [22,23].

In 1991, the new 14-membered macrolides clarithromycin (CAM) and roxithromycin (RXM) were launched in Japan, and clinical studies using low-dose, long-term EM, CAM, or RXM indicated that macrolide therapy is very effective for treating CRS [24,25]. In 2007, the Japan Rhinologic Society proposed guiding principles for the treatment of CRS, and macrolide therapy was strongly recommended [26]. At present, macrolide therapy is a very important and widely used treatment for CRS in Japan. The 15-membered macrolide azithromycin (AZM) exhibits an anti-inflammatory action similar to that of EM, CAM or RXM, and low-dose, long-term AZM treatment has shown good clinical efficacy against chronic airway diseases such as cystic fibrosis in Europe and the United States [27]. However, AZM is not used in macrolide therapy in Japan because the national health insurance program has not approved it for long-term administration. The 16-membered macrolides do not exhibit anti-inflammatory activity.

The first double-blind, randomized, placebo-controlled study of macrolide therapy was reported by Wallwork et al. [28] in 2006. In this study, patients were given RXM (150 mg/day) for 3 months to treat CRS without nasal polyps (CRSsNP). This treatment resulted in improvements in Sinonasal Outcome Test-20 scores, saccharin time, nasal endoscopic findings, and IL-8 levels in nasal lavage fluid. The results were significantly better in the RXM group than the placebo group, and the effects were marked, especially in patients with lower serum IgE levels. Based on the results of this placebo-controlled study, the evidence-based guideline for CRS established by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2007 [29] designated low-dose, long-term macrolide therapy as a grade-A (strong recommendation) treatment for CRSsNP. Macrolide therapy, local steroid treatment, and nasal irrigation in particular are recommended for moderate/severe cases. However, in the EPOS 2012 [30], the grade-A designation for macrolide therapy was reduced to grade C (particularly if IgE is not elevated) based on the results of a double-blind, randomized, placebo-controlled study of AZM (500 mg/week for 3 months) in CRS patients [31]. However, this study included patients with high IgE levels, nasal polyposis, and bronchial asthma, against which macrolide therapy is known to be ineffective.

2. Pathogenesis of CRS and the mechanism of action of macrolide therapy

CRS is a common nasal infectious disease that may or may not involve nasal polyps. Symptoms of CRS include anterior and posterior nasal discharge and nasal obstruction. CRS involves mucus hypersecretion and mucosal inflammation induced by a variety of inflammatory mediators, including the proinflammatory cytokines IL-1β and TNF-α, bacterial products, arachidonic acid metabolites, proteases, and neutrophil/eosinophil products. Excessive mucin production increases the viscoelasticity of mucus, and mucus strands connect the mucus blanket with epithelial goblet cells. Changes in the mucus and damage to the epithelium impair mucociliary transport. Obstruction of nasal passages caused by inflammation of mucosa or nasal polyps and mucociliary dysfunction leads to "mucostasis," the accumulation of stagnant

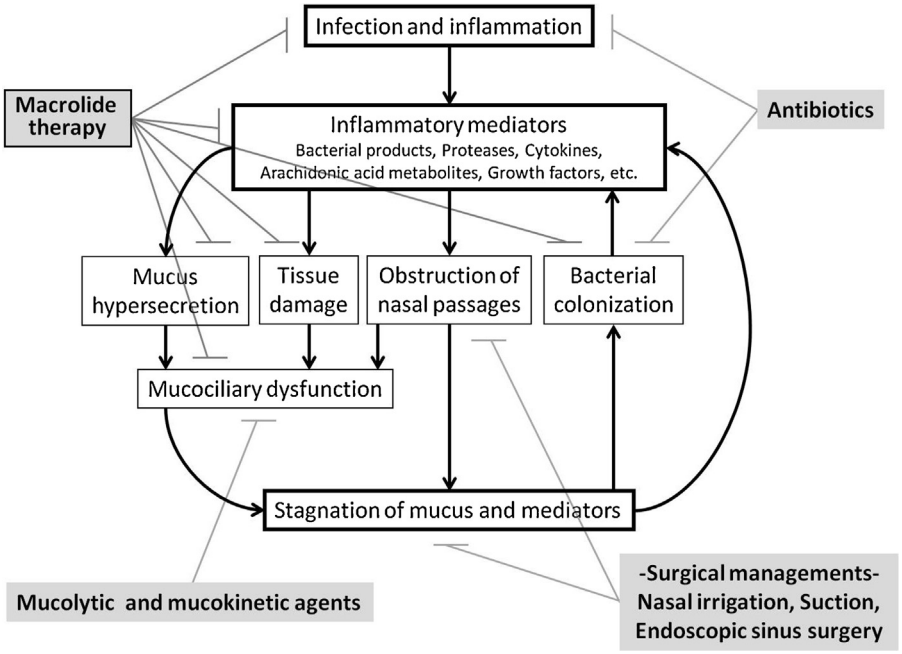

Fig. 1. The vicious cycle of self-mediated inflammation caused by stagnant mucus in CRS. Mucus hypersecretion and damage to the epithelium impair mucociliary transport, resulting in "mucostasis," the accumulation of stagnant, pathologic mucus containing various inflammatory mediators and pathogenic microbes. These mediators and microbes exacerbate the local inflammation, leading to further bacterial colonization. Surgical removal of the stagnant mucus is critical to prevent self-mediated inflammation in CRS patients. The 14- and 15-membered macrolides exhibit a variety of anti-inflammatory and immunomodulatory activities.

Please cite this article in press as: Shimizu T, Suzaki H. Past, present and future of macrolide therapy for chronic rhinosinusitis in Japan. Auris Nasus Larynx (2015), http://dx.doi.org/10.1016/j.anl.2015.08.014