Auris Nasus Larynx 40 (2013) 46–50

Contents lists available at SciVerse ScienceDirect

Auris Nasus Larynx

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

Low dose macrolide administration for long term is effective for otitis media with effusion in children

Kaitian Chen, Xuan Wu, Guangli Jiang, Jintao Du, Hongyan Jiang *

Department of Otorhinolaryngology, the First Affiliated Hospital, Institute of Otorhinolaryngology, Sun Yat-Sen University, Guangzhou 510080, PR China

ARTICLE INFO

Article history:
Received 3 November 2011
Accepted 7 May 2012
Available online 4 June 2012

Keywords:
Otitis media with effusion
Macrolides
Biofilm

ABSTRACT

Objective: To explore the clinical effect and possible mechanism of macrolides on otitis media with effusion in children.
Methods: Children with otitis media with effusion were recruited and prescribed for macrolides according to a designed scheme, and followed up for 8–12 weeks. Middle ear effusion samples were collected from the participants to assess the presence of biofilm.
Results: Macrolides were found to have significant effect on the therapy of early stage otitis media with effusion for 88.7–92.5% of participants compared with 50.9–60.3% in control group after 8–12 weeks. Almost 72.1% of chronic otitis media with effusion patients recovered after an 8 weeks' course low dose macrolides prescription. Biofilm occurred in 30.8% (4/13) of middle ear effusion.
Conclusions: The results indicate that macrolides are effective for otitis media with effusion in children. Bacterial biofilm may play an important role in the pathogenesis of otitis media with effusion.

1. Introduction

As one of the most common diseases in children, otitis media with effusion (OME) is characterized by the presence of fluid in the middle ear without signs or symptoms of acute inflammation. Most doctors suggest 3 months of watchful waiting for children without serious complications due to its self-limited natural history. However, research indicates that the effective rates are typically only between 45% and 52% after 1 and 3 months, respectively, during follow-up in children aged 4–11 [1]. At least half of the children did not recover spontaneously. Similarly, Rosenfeld and Kay [2] found a recovery rate of only 28% in OME of unknown duration, though OME after untreated acute otitis media had 74% resolution rate after 3 months. Chronic OME had only 26% resolution by 6 months and 33% resolution by 1 year. In cases of chronic otitis media with effusion, surgery is recommended [3] as retrieval. This leads us to question whether watchful waiting is really an appropriate treatment option and whether there are any feasible interventions to improve therapeutic efficacy. Is surgery the only approach for children with chronic OME?

The middle ear mucosa of chronic OME was found to have a biofilm structure [4], which could protect bacteria from medication. Consequently, refractory inflammations occur when the bacteria scatter outside the biofilm [4]. This may explain, in part, why many children with OME could not recover spontaneously.

As we known, macrolides, a long-term medication for chronic rhinosinusitis [5], have anti-biofilm and anti-inflammatory function [6] through the inhibition of the NF-κB system [7–11]. We therefore conducted a prospective trial to investigate the clinical efficacy of macrolides in otitis media with effusion in children. Bacterial biofilm, a possible target of macrolides on OME, was also assessed.

2. Patients and methods

Patients aged between 3 and 14 years old with otitis media with effusion were recruited to this prospective study from June 2009 to March 2011 in the department of ENT in the First Affiliated Hospital, Sun Yat-Sen University. Middle ear effusion of patients was taken by tympanocentesis. The participants' guardians were informed and gave consent for the children to take part in this research. The institutional review board of the First Affiliated Hospital, Sun Yat-Sen University reviewed and approved the research.

The inclusion criteria for otitis media with effusion were as followed: aural fullness, hearing loss or tinnitus; integrity, invagination or fluid level of tympanic membrane; and type B or C2 tympanogram. Children were excluded if they had the following: suppurative otitis media; tympanic membrane perforation; adenoid hypertrophy; tumor; severe systemic diseases and allergy or intolerance to macrolides. The diagnosis criterion for rhinosinusitis is defined as inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or

* Corresponding author. Tel.: +86 87333733; fax: +86 87333733.
E-mail address: hyjiangus@163.com (H. Jiang).

0385-8146/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.anl.2012.05.008

nasal discharge (anterior/posterior nasal drip) [5]. Participants were allocated to early stage OME (duration less than 3 months) or Chronic stage OME (duration more than 3 months) groups, respectively.

As to early stage OME, involved subjects were randomly divided into two subgroups: the macrolides group and the control group. The macrolides group were prescribed a full dose of clarithromycin (15 mg/kg/d bid daily) in the first week, then changed to a low dose (5–8 mg/kg/d qd) until the tympanogram was type "A", along with being prescribed a topical glucocorticosteroid nasal spray. After the effusion resolved, low dose clarithromycin were further continued for 1 week, then the medication finished. The whole medication course was less than 12 weeks. Patients in the control group were given topical glucocorticosteroid nasal spray only for 12 weeks.

The chronic stage of OME patients were directly prescribed a low dose of macrolides clarithromycin (5–8 mg/kg/d bid daily) until the tympanogram was type "A", and further lasted for 1 week before the treatment finished. The whole medication course was no more than 8 weeks. All participants were followed up every 2 weeks with hearing and tympanogram examinations. Routine nasal endoscopy was taken to exclude possible nasal diseases (in particular, adenoid hypertrophy). The criteria used to assess the effectiveness of treatment were referenced as Williamson et al. [1]. "Cure" was defined as type A tympanogram. "Improved" was used for change from type B or C2 to C1 tympanogram; "effective" was calculated as "cure" plus "improved". "Ineffective" was used for B type or no change tympanogram (type C2 to C2).

Middle ear effusion was collected from patients by tympanocentesis and stored in a sterilized EP tube. Middle ear effusion was centrifuged at 1300 × *g* for 10 min, and the supernatant was transferred to a new tube. The remainder was fixed in the slides with 4% paraformaldehyde and stored for the detection of biofilm.16S rRNA fluorescence in situ hybridization (FISH) was performed as described by Manz et al. [12]. Samples were fixed with 4% paraformaldehyde on the slides and then washed with PBS three times for 3 min each wash. There were dehydrated with 75% and 95% alcohol for 5 min each, and then incubated 100 μl lysozyme solution (in 0.1 M Tris–0.05 M Na_2 EDTA) for 15 min at 37 °C, and washed with PBS. After the wash, 20 μl hybridization solution (0.9 M NaCl, 20 mM Tris–HCl [pH7.5–7.6], 0.01% SDS and 20–25% formamide) was added to each sample for prehybridization at 46 °C for 15 min and 100 ng each of four specific bacterial probes with fluorescence were added to the samples and hybridization solution. Bacterial probes were designed as EUB 5′-GCTGCCTCCCGTAGGAGT-3′ (16S [338–355]) [13], eubacteria with cy3 labeled at the 5′-end; Spn 5′-GTGATGCAAGTGCACCTT-3′ (16S [195–212]) [14], *S. pneumoniae*, with FAM labeled at the 5′-end; H.inf 5′-CCGCACTTTCATCTCCG-3′ (16S [185–202]) [15], *H. influenzae*, with FAM labeled at the 5′-end; M.cat 5′-CCGCCACUAAGUAUCAGA-3′ (16S [88–105]) [4] (*M. catarrhalis*), with FAM labeled at the 5′-end. Probes were synthesized by Sangon (Shanghai, China). Hybridization were performed at 46 °C for 180 min in a humidified hybridization chamber, and 40 μl washing buffer (20 mM Tris–HCl [pH 7.5–7.6], 5 mM EDTA, 0.01% SDS, 200 mM NaCl) was added for 15 min at 48 °C. Samples were then stained with DAPI (1 μg/ml) for 5 min, washed with PBS and air-dried. The slides were then examined for expression of fluorescence with a Leica microscope (Leica, Germany).

The biofilm percentages are presented as percentile % (*n*). Age, duration of treatment, and hearing level are described as mean ± standard deviation. A chi-squared test was used for comparison of effective rates among groups. SPSS software 13.0 was used to analyze the data and a difference between variables was considered statistically significant if $P < 0.05$.

3. Results

3.1. Early stage OME

Eighty-four children were recruited (49 male and 35 female; 121 ears in total). Six patients in the macrolides group and five children in control group chose to quit the research during follow-up and were excluded in the results (Fig. 1). Patients' ages ranged from 3 years to 11 years with a mean of 67.8 ± 23.1 months for the control group and 67.7 ± 22.3 months for the macrolides group. The duration of disease varied from 1 day to 5 weeks, with a mean of 11.1 ± 6.45 days for the control group and 10.2 ± 6.58 days for the macrolides group. Total 106 ears were enrolled composing of 83 type B and 23 type C2 tympanogram. The average air-bone gap was 30.6 ± 7.82 dB in the control group and 31.7 ± 6.83 dB in the macrolides group. The differences between the groups were not statistically significant (Table 1). Four participants in macrolides groups and two participants in control group suffered from rhinosinusitis simultaneously before treatment.

All the rest patients completed the entire course of treatment. The medication course ranged from 5 to 12 weeks (9.91 ± 2.41 weeks). Two children in macrolides group received azithromycin therapy alternatively and were both cured by the eighth week. The effective rates were 28.3%, 64.2%, 88.7%, 92.5% and 92.5% for the macrolides group, compared with 22.6%, 45.3%, 50.9%, 56.6% and 60.3% for the control group during the 4th, 6th, 8th, 10th and 12th week of treatment. The results were statistically significantly different between the two groups (Table 2 and Fig. 2). 25 ears (17 children, Fig. 1) including 3 type B and 22 type C2 tympanogram were ineffective. Hearing levels (air-bone gap) were improved to 8.72 ± 7.52 dB and 14.1 ± 8.76 dB in macrolides group and control group, respectively. These results were statistically significantly different ($P < 0.01$). Three children (four ears) in macrolides group were arranged for tympanostomy tube insertion for their failure to macrolides treatment.

Side effects were also recorded. In macrolides group, one child had vomiting, one child had acute otitis media and two children suffered from acute rhinosinusitis during treatment. The side effect rate for macrolides was 11.1% (4/36). Relapses of acute otitis media occurred in four children who withdrawed voluntarily without full course macrolides medication.

3.2. Chronic stage OME

Twenty-six children (13 males and 13 females, 43 ears) were recruited to the Chronic OME group. Their ages ranged from 3 to 11

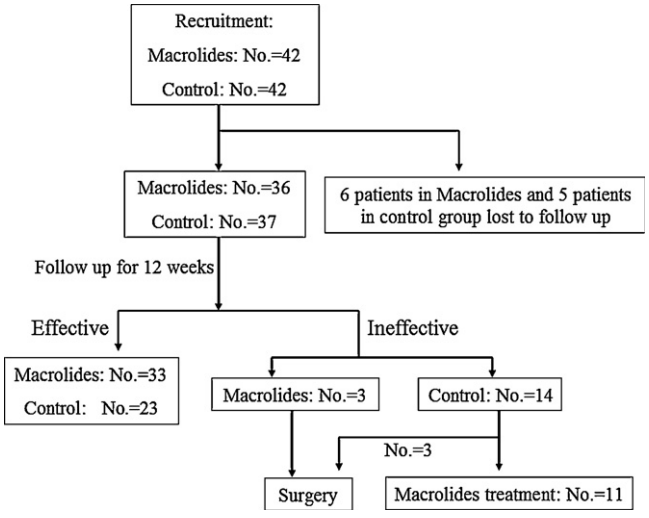

Fig. 1. Flowchart of macrolides treatment clinical trial in early stage OME.