Original Article

Recurrent Acute Rhinosinusitis Prevention by Azithromycin in Children with Nonallergic Rhinitis

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What is already known about this topic? Recurrent acute rhinosinusitis (RARS) has a considerable impact on quality of life and impairment of daily function. Role of antibiotics to prevent RARS in children with nonallergic rhinitis (NAR) has not been investigated.

What does this article add to our knowledge? Azithromycin prophylaxis can reduce the number of rhinosinusitis episodes and medication score, and improve nasal symptoms in NAR children with RARS. The number needed to treat using azithromycin prophylaxis to prevent 1 patient from having RARS was 2.

How does this study impact current management guidelines? These data support the efficacy of azithromycin prophylaxis to prevent RARS in children with NAR.

BACKGROUND: Recurrent acute rhinosinusitis (RARS) is characterized by multiple episodes of acute rhinosinusitis between which symptoms and signs resolve completely. The role of antibiotic prophylaxis to prevent RARS in children with nonallergic rhinitis (NAR) has not been investigated.
OBJECTIVE: To evaluate the effect of azithromycin to prevent RARS in children with NAR.
METHODS: A randomized, double-blind, placebo-controlled study was conducted in NAR children (5-15 years) with RARS. Azithromycin (5 mg/kg/d) 3 d/wk for 12 months or placebo was assigned to the study group and the control group, respectively. Patients with allergic rhinitis were excluded. Number of rhinosinusitis episodes in 12 months, visual analog scale score of nasal symptoms, and adjunctive medication score were recorded.
RESULTS: Forty patients were enrolled and 20 patients were assigned randomly to the azithromycin and placebo groups. IgG subclass and specific antibody deficiencies were found in 83% and 2.5% of patients, respectively. After 12 months, the number of rhinosinusitis episodes/y in the azithromycin group reduced significantly from 5 to 0.5 ($P < .001$) in contrast to the placebo group. Number needed to treat using azithromycin prophylaxis to prevent 1 patient from having RARS was 2. The average visual analog scale score and the average adjunctive medication score in the azithromycin (but not in the placebo) group reduced significantly compared with baseline (2.2 ± 1.4 vs 5.4 ± 1.8) and (3.9 ± 1.7 vs 5.4 ± 1.1), respectively ($P < .001$).
CONCLUSIONS: Azithromycin prophylaxis can reduce the number of rhinosinusitis episodes and medication score, and improve nasal symptoms in NAR children with RARS. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Azithromycin; Children; Nonallergic rhinitis; Recurrent acute rhinosinusitis; Rhinitis; Sinusitis; Prevention*

Pediatric rhinosinusitis is a common medical problem. In children, it is estimated that 5% to 10% of upper respiratory tract infections (URIs) are complicated by acute rhinosinusitis (ARS) and that 6% to 13% of all children develop rhinosinusitis by the age of 3 years.[1] Early recognition and adequate management are the main strategies to improve outcome. Pediatric rhinosinusitis is categorized as acute, subacute, or chronic. ARS lasts 10 to 30 days, subacute rhinosinusitis lasts 4 to 12 weeks, and chronic rhinosinusitis (CRS) lasts more than 12 weeks.[2] Recurrent acute rhinosinusitis (RARS) is characterized by multiple episodes of ARS where the symptoms and signs of infection resolve completely between episodes.[3,4] RARS and CRS have been found in 11.5% and 18.9% of cases of pediatric rhinosinusitis, respectively.[5] Children with CRS or RARS need a prolonged course of antibiotics and frequent health care utilization. These conditions have a considerable impact on quality of life and impairment of daily function.[6-8]

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Abbreviations used
AMS- adjunctive medication score
AR- allergic rhinitis
ARS- acute rhinosinusitis
CF- cystic fibrosis
CRS- chronic rhinosinusitis
NAR- nonallergic rhinitis
RARS- recurrent acute rhinosinusitis
URI- upper respiratory tract infection
VAS- visual analog scale

RARS and CRS are uncommon conditions in healthy children. Hence, children should be evaluated for underlying diseases such as allergic rhinitis (AR) and nonallergic rhinitis (NAR), immunodeficiency, ciliary dysfunction, gastroesophageal reflux, and anatomical abnormalities of the osteomeatal complex (including septal deviation, nasal polyps, and concha bullosa).[5,9-11] Several strategies have been suggested to prevent RARS: adequate duration of antibiotics; saline irrigation; avoidance of exposure to smoke; reduced attendance at daycare centers; vaccines against influenza and *Haemophilus influenzae* type b; removal of adenoids; and treatment of underlying factors (eg, AR, gastroesophageal reflux, and anatomical obstruction).[11-14] A prolonged course of antibiotics in CRS has been associated with beneficial outcome in several reports.[15,16]

A prospective randomized controlled trial to determine the efficacy of prophylactic antibiotics for RARS in children is lacking. The objective of the present study was to evaluate the effect of azithromycin to prevent RARS in children with NAR. Patients with AR were excluded because the most specific therapy for moderate-to-severe AR is allergen immunotherapy.

METHODS

Study design

This was a 12-month prospective, randomized, double-blind, placebo-controlled study (Figure 1). The study protocol was approved by the Institutional Review Board of Siriraj Hospital (Mahidol University, Bangkok, Thailand; approval code: 394/2551(EC4)). Written informed consent was obtained from the parents/guardians of each child.

Participants

Children aged 5 to 15 years diagnosed as having RARS in pediatric allergy clinic and otorhinolaryngology clinic at Siriraj Hospital were recruited. The number of rhinosinusitis episodes was determined from medical records. *ARS* was defined as persistent symptoms of a URI lasting more than 10 days but less than 30 days, or worsening symptoms of a URI after initial improvement, or severe symptoms at onset (purulent nasal discharge for 3-4 days with high fever).[3,4,17] *RARS* was defined as 3 episodes of ARS in 6 months or 4 episodes in 12 months, each lasting less than 30 days and separated by intervals of 10 days or more during which the patient was asymptomatic.[3,4] Patients who had CRS (symptoms of rhinosinusitis lasting more than 90 days and asymptomatic less than 10 days between episodes of rhinosinusitis),[3,4] AR, a history of allergic reactions to azithromycin or macrolides, or underlying diseases (eg, chronic renal diseases, liver diseases, or cardiovascular diseases) were excluded from this study, as were patients who received other preventive therapy (eg, nasal irrigation with gentamicin or intravenous immunoglobulin).

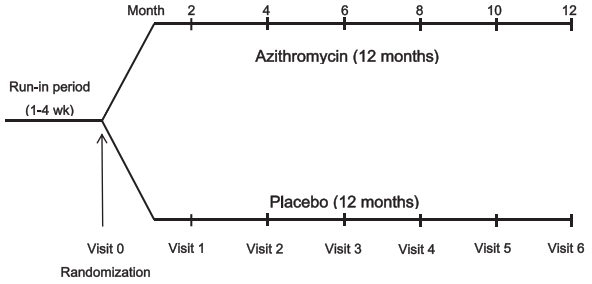

FIGURE 1. Overview of the study design.

Interventions

Patients in the "active" group received azithromycin oral suspension (5 mg/kg body weight/d; Zithromax; Pfizer, New York, NY) on 3 nonconsecutive days per week (eg, Monday, Wednesday, and Friday) for 12 months. A placebo was prepared by a pharmacist (T.T.), and was identical to the oral suspension of azithromycin in appearance, texture, smell, taste, labeling, and packaging. Before administration, the oral powder of the trial medication was reconstituted with 9 mL of water in a bottle to give a total volume of 15 mL per bottle. The viscosity of the placebo was identical to that of azithromycin after reconstitution. A 12-month period was designed to overcome the seasonal variation of URI. Patients were asked to return the bottle at each visit to ensure compliance.

All patients were instructed to use normal saline nasal irrigation. They were allowed to use adjunctive medications for relief of rhinitis symptoms if needed (eg, intranasal corticosteroids, oral antihistamines, oral leukotriene receptor antagonists, and oral decongestants). Patients and their parents were instructed to keep a diary during the study period, for a daily evaluation of nasal symptoms and adjunctive medications.

During the study period, all patients were instructed to come to the pediatric allergy clinic or pediatric outpatient clinic for any illness and they were evaluated by J.V. The patients who had ARS, defined by the American Academy of Pediatrics criteria,[3,4] were documented and treated with antibiotic therapy (excluded azithromycin) for 10 to 14 days. The azithromycin prophylaxis was stopped during that period and restarted after the treatment of ARS.

Randomization

Block-of-four randomization was used for allocation sequencing of patients using numbered containers. T.T. and O.J. generated the allocation sequence and assigned patients to their groups. J.V. enrolled patients and assessed outcomes. J.V. and patients were blinded to group assignment from the beginning of assignment to the end of interventions. Interventions were decoded at the end of the study by O.J.

Procedures

In the run-in period, all children were evaluated for allergic sensitization and immune function. Serum IgG, IgA, IgM as well as IgG subclass and antibody responses to pneumococcal immunization were assessed. The skin prick test was done with a panel of the most prevalent local aeroallergens: house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*); American and German cockroaches; dander from cats and dogs; grass pollens (Bermuda, Johnson); Acacia; and careless weeds and molds (*Alternaria* spp, *Cladosporium* spp, *Penicillium* spp, *Aspergillus* spp, and *Fusarium* spp). Commercial allergens from ALK-Abello (Port

Washington, NY) were used. Histamine hydrochloride (10 mg/mL) and physiologic (0.9%) saline were used as positive and negative controls, respectively. A positive skin prick test result was defined as a wheal diameter of 3 mm or more to at least 1 of these aeroallergens. Patients who had a negative skin prick test result to all aeroallergens were recruited. Serum levels of IgG, IgA, IgM, as well as IgG subclasses were measured by nephelometry using reagents and an automated system (Siemens, Erlangen, Germany). Deficiency of IgG subclasses was defined using low-level criteria (<2 SDs of normal levels for age) or low-percentage criteria (<60%, <20%, <5%, and <1% of IgG_1, IgG_2, IgG_3, and IgG_4, respectively).[18] Antibody titers to pneumococcal capsular polysaccharide (4, 6B, 7F, 9N, 9V, 14, 18C, and 23F) were measured in serum samples obtained before and 4 to 6 weeks after immunization using an ELISA. Adequate response to individual pneumococcal serotype was defined as a postimmunization antibody concentration of 1.3 μg/mL or higher, or a 4-fold increase over the preimmunization value. Specific antibody deficiency was defined as a satisfactory response to less than 50% of the serotypes tested in children between 2 and 5 years, and less than 70% of the serotypes tested in children older than 5 years.[19,20]

Primary and secondary outcomes

The primary outcome was the number of episodes of rhinosinusitis in 12 months. Secondary outcomes were the visual analog scale (VAS) score and adjunctive medication score (AMS). The daily VAS score was used to assess nasal symptoms (rhinorrhea, nasal congestion, sneezing, nasal pruritus, snoring, and postnasal drip), which were graded every day by patients in a diary using an 11-point rating scale (0 = no symptoms to 10 = severe symptoms) for all combined nasal symptoms.[21,22] The average VAS score was the average of the daily VAS score during the period of observation. The daily AMS for each patient was calculated as the sum of adjunctive medication administered on a particular day. Scores were assigned to different medications: 0 = no rescue medication was taken; 1 = patient took oral antihistamines; 2 = patient took oral leukotriene receptor antagonists or oral decongestants; 3 = patient took intranasal corticosteroids.[23,24] The average AMS was the average of the daily AMS during the period of observation.

Adverse events

Adverse events were documented throughout the study by asking the parents/guardians of the children at each assessment about events associated with administration of the study medication.

Statistical analyses

Calculation of sample size was based on a preliminary study, which showed that the number of rhinosinusitis episodes was 0.6 ± 0.3 per month per patient with recurrent rhinosinusitis. After using azithromycin prophylaxis, it was presumed that effective treatment would reduce the number of rhinosinusitis episodes by 50%. Using 80% power, an alpha value of 0.05, and a beta value of 0.2, the sample size for each group was estimated to be 17 patients. Allowing for a prevalence of withdrawal of approximately 20%, 20 patients were recruited in each group.

Baseline characteristics of patients in the active and placebo groups were analyzed using descriptive statistics (frequency, mean, median, SD, and range), the chi-square test, and the Mann-Whitney *U* test. Comparison between the number of rhinosinusitis episodes per year in the active and placebo groups was done using the Mann-Whitney *U* test and Wilcoxon signed-rank test. Between-group differences in the average VAS score and the average AMS were calculated using the independent-sample *t* test. Within-group differences in the average VAS score and the average AMS were calculated using the paired-sample *t* test. The number needed to treat was also calculated. A *P* value of less than .05 was considered significant.

RESULTS

Participants

The study was conducted between January 2010 and June 2015. One hundred children with RARS were screened; 59 were not eligible, and 1 declined to participate (Figure 2). Hence, 40 patients were enrolled into the study. Twenty patients were assigned randomly to azithromycin and placebo groups, respectively. All patients were reported to receive an influenza vaccine every year. No patient had an infection other than sinusitis (eg, pneumonia, bronchiectasis, or otitis media).

The 2 groups were homogeneous with respect to baseline demographic data, including age, sex, number of rhinosinusitis episodes, and immune function (Table I). Thirty-three patients (83%) had an underlying IgG subclass deficiency, and 1 patient (2.5%) had an underlying specific antibody deficiency. The baseline average VAS score in the azithromycin group was significantly higher than that in the placebo group ($P = .02$), whereas the baseline average AMS in the azithromycin group was not significantly different from that in the placebo group ($P = .07$). At follow-up, 40 patients (20 in each group) completed the study (Figure 2).

Number of rhinosinusitis episodes

The number of rhinosinusitis episodes per year in the azithromycin and placebo groups at baseline and after study completion is shown in Figure 3. The number of rhinosinusitis episodes per year in the azithromycin group was reduced significantly after 12 months of intervention (median, 0.5; range, 0-6.0) compared with baseline (median, 5.0; range, 4.0-7.0) (difference, −4.0; 95% CI, −5.0 to −3.0; $P < .001$). The number of rhinosinusitis episodes per year in the placebo group was not reduced significantly (median at baseline, 4.0, and range, 4.0-6.0; median at trial completion, 4.0, and range, 0-6.0) (difference, 0.0; 95% CI, −2.0 to 0.0; $P = .09$). The reduction in number from the baseline value was significantly different in the azithromycin group compared with the placebo group ($P < .001$). The number needed to treat using azithromycin to prevent 1 patient suffering from RARS was 2.

Patients who had a reduction in the number of sinusitis episodes of more than 50% were designated as "responders." Responders were found in 85% (17 of 20) of the azithromycin group and 25% (5 of 20) of the placebo group (difference, 60.0%; 95% CI, 29.7%-76.9%; $P < .001$). In the azithromycin group, 15 of 17 (88%) responders had an underlying immunodeficiency. Age, sex, or immunodeficiency status were not predictors of a favorable response to azithromycin ($P > .05$).

In addition, the number of antibiotic courses given during the study period in the azithromycin group was significantly less than that in the placebo group (median, 0.5, and range, 0-6.0, vs median, 4.0, and range, 0-6.0; $P < .001$).

VAS score and AMS

The average VAS score in the azithromycin group was reduced significantly after 12 months of intervention (2.2 ± 1.4) compared with baseline (5.4 ± 1.8) (mean difference, −3.2 ± 2.6;

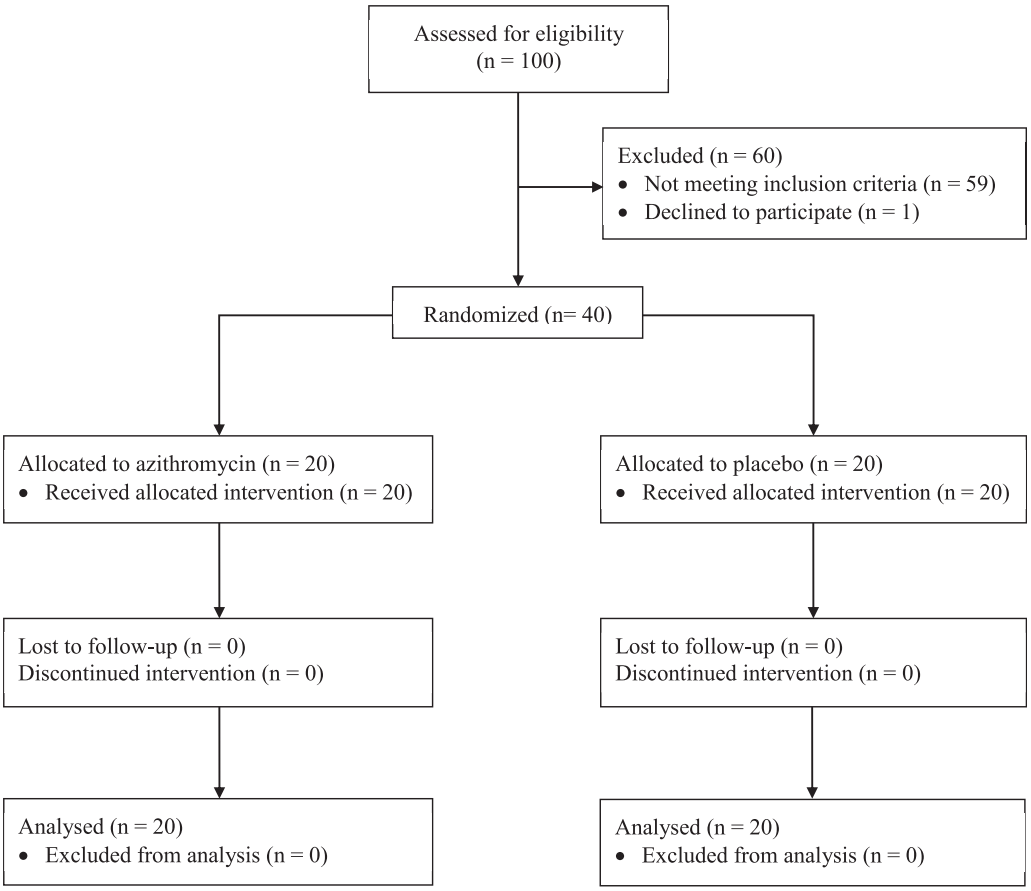

FIGURE 2. Flow diagram of the study.

TABLE I. Baseline characteristics

Characteristic	Azithromycin (n = 20)	Placebo (n = 20)	Difference (95% CI)	*P*
Age (y), median (range)	5.8 (5.0 to 9.2)	5.9 (5.0 to 12.3)	−0.1 (−0.9 to 0.5)	.72
Sex: male, n (%)	15 (75.0)	12 (60.0)	15.0 (−13.4 to 40.4)	.31
No. of rhinosinusitis per year, median (range)	5 (4.0 to 7.0)	4 (4.0 to 6.0)	1.0 (0.0 to 1.0)	.09
IgG subclass deficiency, n (%)	17 (85.0)	16 (80.0)	5.0 (−19.2 to 28.7)	.47
Isolated IgG_3 subclass deficiency	6 (30.0)	10 (50.0)		
$IgG_{2,3}$ subclass deficiency	7 (35.0)	2 (10.0)		
$IgG_{1,3}$ subclass deficiency	2 (10.0)	1 (5.0)		
Isolated IgG_2 subclass deficiency	1 (5.0)	2 (10.0)		
Isolated IgG_1 subclass deficiency	1 (5.0)	1 (5.0)		
Specific antibody deficiency, n (%)	0 (0.0)	1 (5.0)	−5.0 (−23.6 to 11.6)	1.0
Baseline average VAS, mean ± SD	5.4 ± 1.8	4.0 ± 1.8	1.4 (0.2 to 2.6)	.02
Baseline average AMS, mean ± SD	5.4 ± 1.1	4.7 ± 1.2	0.7 (−0.1 to 1.4)	.07

95% CI, −4.3 to −2.0; $P < .001$). The average AMS in the azithromycin group was also reduced significantly after 12 months of intervention (3.9 ± 1.7) compared with baseline (5.4 ± 1.1) (mean difference, −1.5 ± 1.4; 95% CI, −2.2 to −0.9; $P < .001$). The average VAS score in the placebo group was not reduced significantly after 12 months of intervention (4.6 ± 1.3) compared with baseline (4.0 ± 1.8) (mean difference, 0.6 ± 2.0; 95% CI, −0.3 to 1.6; $P = .16$). The average AMS in the placebo group was not reduced significantly after 12 months of intervention (4.5 ± 1.0) compared with baseline (4.7 ± 1.2) (mean difference, −0.2 ± 0.5; 95% CI, −0.5 to 0.4; $P = .09$). The reduction from baseline in the average VAS score and the average AMS was significant in the azithromycin group (mean difference, −3.8 ± 0.7; 95% CI, −5.3 to −2.3; $P < .001$) compared with the placebo group (mean difference, −1.3 ± 0.3; 95% CI, −2.0 to −0.6; $P = .001$, respectively) (Table II).

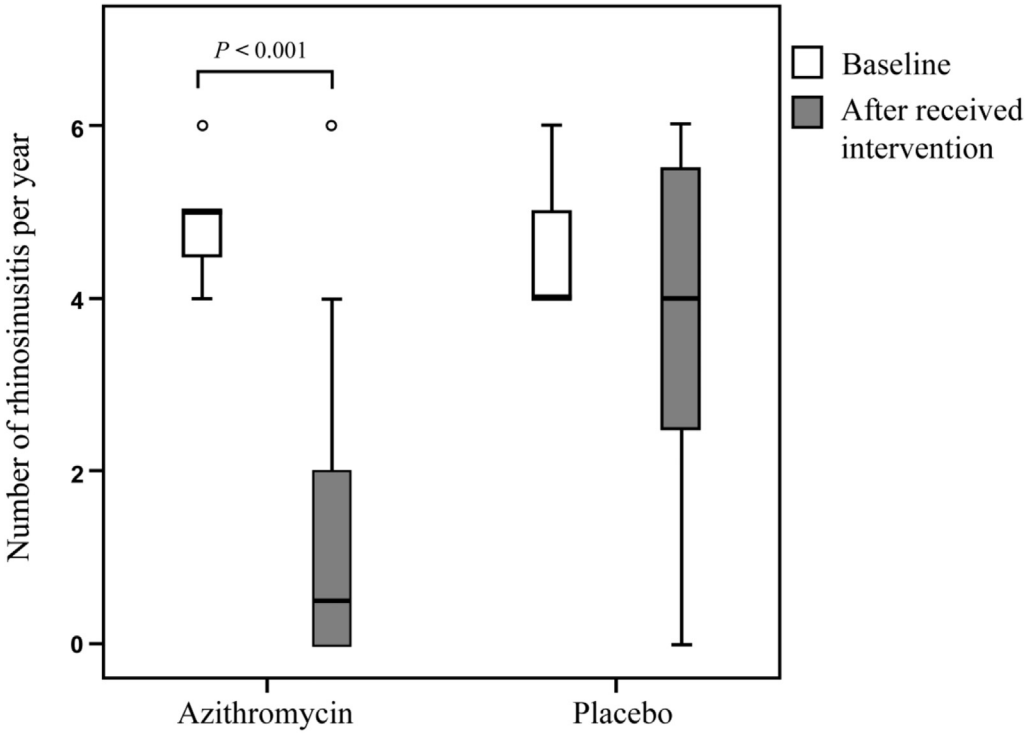

FIGURE 3. Number of rhinosinusitis episodes per year in the azithromycin and placebo groups before and after intervention.

TABLE II. Comparison between the VAS score and AMS in azithromycin and placebo groups

Outcome	Azithromycin (n = 20)	Placebo (n = 20)	Mean difference (95% CI)	*P*
Change from baseline in average VAS score, mean ± SD	−3.2 ± 2.6	0.6 ± 2.0	−3.8 ± 0.7 (−5.3 to −2.3)	<.001
Change from baseline in average AMS, mean ± SD	−1.5 ± 1.4	−0.2 ± 0.5	−1.3 ± 0.3 (−2.0 to −0.6)	.001

Adverse events

Azithromycin and placebo interventions were tolerated equally well. Adverse events (allergic reactions, diarrhea, nausea, vomiting, abdominal pain, dizziness, headache, cardiovascular events, oral candidiasis, or serious infections) were not reported in either group.

DISCUSSION

Antibiotic prophylaxis has been studied for its potential benefit in several conditions (eg, bronchiectasis, otitis media, and CRS) in addition to various immunodeficiency diseases.[16,25-28] Ragab et al[15] compared erythromycin with surgery in 90 patients with CRS and found that both treatments elicited similar improvements in symptom scores and endoscopic findings at follow-up. They suggested that CRS should be treated initially with aggressive medical treatment before a decision is made regarding surgical intervention. Wallwork et al[16] conducted a trial of roxithromycin (150 mg/d) *versus* placebo for 3 months in 64 patients with CRS and demonstrated that patients in the antibiotic group (but not those in the placebo group) had a significant improvement in sinonasal outcome and nasal endoscopy. In contrast, Videler et al[29] designated patients with recalcitrant CRS with or without nasal polyps unresponsive to optimal medical treatment and surgical therapy to receive either azithromycin or placebo. Azithromycin was given at 500 mg for 3 days during the first week, followed by 500 mg per week for the next 11 weeks. Fifty-eight percent of the patients had undergone revision sinus surgery and 52% had a nasal polyp. No significant benefit was found in the treatment group compared with the placebo group. Authors stated that treatment failure could have been due to disease severity or underdosing of azithromycin.[29] In addition, nasal polyposis and severe CRS on computed tomography suggested a poor response to macrolide therapy.[25]

Gandhi et al[30] studied the effect of amoxicillin (20 mg/kg/d) for 1 year as prophylaxis in 26 children with CRS and showed a 50% reduction in the number of episodes of sinusitis in 74% of subjects. There were no significant differences in age, sex, atopy, or presence of a B-cell immune abnormality in "good" *versus* "poor" outcome groups.[30] Veskitkul et al[31] retrospectively described 94 children with RARS and showed that 69% of children received preventive therapy, of whom 61.5% received oral antibiotic prophylaxis, 33.8% underwent adenotonsillectomy, 18.5% received immunotherapy against a specific allergen, 16.9% underwent nasal irrigation using gentamycin, and 9.2% received intravenous immunoglobulin. All patients who received immunotherapy had been diagnosed with AR. Up to 13.8% of children with RARS had a spontaneous remission.

The present study demonstrated that azithromycin prophylaxis can significantly reduce the incidence of rhinosinusitis and

medication scores, as well as improve nasal symptoms, in NAR children with RARS. Azithromycin was chosen because of its anti-inflammatory and immunomodulatory activity.[32,33] The selected dose was based on the recommended antibiotic prophylaxis for primary antibody deficiencies.[25] With a number needed to treat of 2, this regimen of antibiotic prophylaxis seems to be an attractive choice for NAR children with RARS.

Underlying conditions for CRS and RARS have been investigated in several studies. Shapiro et al[34] studied 61 children with CRS referred to an allergist for allergy and immunology workup. They found that 36% of subjects had a positive skin test result to inhalant allergen and 56% had low IgG or a poor antibody response to a polysaccharide vaccine or both.[34] Gandhi et al[30] evaluated 86 children with CRS. They found that 29% of patients had a B-cell abnormality of an immunoglobulin isotype, IgG subclass, and/or hyporesponsiveness to a pneumococcal polysaccharide vaccine. Eleven of 17 patients who were hyporesponsive to the pneumococcal polysaccharide vaccine had normal immunoglobulin isotypes and IgG subclasses.[30] Veskitkul et al[31] found that the most common predisposing factor for RARS in children was a deficiency in an IgG subclass (78.7%), followed by NAR (64.9%) and AR (35.1%).

In the present study, most patients had a deficiency in an IgG subclass that did not justify monthly use of intravenous immunoglobulin. The practice parameter for the diagnosis and management of primary immunodeficiency suggests that milder antibody deficiencies (eg, selective deficiency of IgA, deficiency of an IgG subclass, deficiency of a specific antibody, or transient hypogammaglobulinemia of infancy) can be treated with antibiotic prophylaxis.[35] However, our study did not have the power to find the predictor of response to prophylaxis using azithromycin because it was not designed for this purpose.

A major concern with the use of antibiotic prophylaxis is the development of antimicrobial resistance among the microbiota. Long-term macrolides were widely used in cystic fibrosis (CF) or non-CF bronchiectasis based on improving pulmonary function and reducing exacerbation.[25] In the past decade, the increasing evidences of antibiotic-resistant bacteria in patients with bronchiectasis on prophylactic antibiotic were reported. A study in pediatric patients with CF showed that long-term azithromycin in these patients significantly increased macrolide-resistant *Staphylococcus aureus* in almost all carriers.[36] In a study by Hansen et al,[37] long-term, low-dose azithromycin in patients with CF showed significantly reduced prevalence of *S aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, but increased macrolide resistance in *S aureus* only.[37] In a recent multicenter trial, children with bronchiectasis were randomized to weekly azithromycin or placebo for 24 months.[38] Nasopharyngeal carriage of *H influenzae* and *Moraxella catarrhalis* decreased significantly in the azithromycin group compared with the placebo group, whereas macrolide-resistant *S pneumoniae* and *S aureus* carriage increased significantly. Interestingly, children with high adherence in the azithromycin group were associated with lower carriage of any pathogen and fewer macrolide-resistant pathogens. In the follow-up swab (median 6 months after the treatment), macrolide-resistant *S pneumoniae* declined significantly in the azithromycin group, but *S aureus* remained 100% macrolide resistant. This study provided important information that the adherence to prophylactic macrolide may limit macrolide resistance by decreasing carriage. The reduction in macrolide-resistant *S pneumoniae* after the cessation of prophylactic antibiotic was reassuring that macrolide resistance was transient. Our study showed that a 12-month course of azithromycin prophylaxis was effective in preventing RARS in children with NAR. After that, we suggested to discontinue azithromycin and monitor the clinical of RARS in these patients to prevent macrolide resistance.

In conclusion, prophylaxis using azithromycin was beneficial in reducing the number of rhinosinusitis episodes and medication score as well as improving nasal symptoms in NAR children with RARS.

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