ORIGINAL CONTRIBUTION

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A study of poor responders for long-term, low-dose macrolide administration for chronic sinusitis*

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SUMMARY

Purpose: *We investigated the clinical factors (CT images, endoscopic nasal findings and allergic factors) involved in resistance of chronic sinusitis to macrolide therapy (ME) retrospectively.*

Methods: *ME was administered for 8-20 weeks in 68 adults with chronic sinusitis cases. The effect was evaluated in each factor from radiographic findings (R0 - R3 according to the severity of the images), nasal findings (N0: no polyp, N1: a single polyp and N2: multiple polyps), allergic factors (A0: no allergy, A1: nasal allergy, A2: bronchial asthma) and objective nasal symptoms. In addition, an effect after polypectomy and histological examination were assessed for N1 and N2 groups.*

Results: *ME was effective in 70.6% (48/68 patients). The efficacy of ME was significantly less in the polyp group compared with the polyp-free group ($p < 0.05$). Therapeutic efficacy was significantly different between R1 and R3 groups ($p < 0.05$) with a tendency for worse outcome from R1 to R3. The efficacy in asthma patients was significantly less compared with patients with allergic rhinitis or no allergy ($p < 0.05$). The efficacy after polypectomy was significantly improved in N2 group but not in N1 group. The number of eosinophil/total inflammatory cells (%) in nasal polyps of resistant cases was significantly higher than in marked improved cases.*

Conclusion: *The efficacy of ME was less in patients with polyposis; CT scans indicating severe findings, bronchial asthma and polyps with increased eosinophil infiltrations. Polypectomy resulted in significant improvement in the efficacy of ME.*

Key words: Macrolide therapy, nasal polyp, CT images, polypectomy, bronchial asthma, eosinophil

INTRODUCTION

Recent years have seen numerous reports by Japanese investigators regarding the efficacy of long-term, low-dose therapy using 14-membered ring macrolides in the treatment of chronic sinusitis. For example, 12-week administration of clarithromycin brought about improvement in the symptoms and rhinoscopic findings in 71.1% of chronic sinusitis patients [(1)]. Another report documented that long-term, low-dose administration of macrolides brought about significant improvement in the nasal symptoms and rhinoscopic findings in patients who had not improved in response to earlier sinus surgery or systemic steroid/antibiotic treatment [(2)]. Roxithromycin administered at 150 mg/day for at least 8 weeks was reported to bring about shrinkage (reduction) of nasal polyps in 52% of patients [(3)]. Clarithromycin administered at 400 mg/day for 8~12 weeks resulted in marked shrinkage of polyps in 40% of patients [(4)].

There have also been many reports regarding the pharmacological actions of macrolides. Those reported actions include breakup of bacterial biofilms [(5,6)], promotion of ciliary movement [(7)], suppression of secretion of glycoconjugates (mucin) [(8,9)], suppression of production of cytokines (IL-8 [(6,10)] and IL-1β [(11)]), inhibition of proliferation of nasal polyp fibroblasts [(12)], etc.

A double-blind and randomized trial of macrolide therapy for chronic sinusitis was conducted by Wallwork et al. [(13)]. They suggested that there were statistically significant improvements in SNOT-20 score, nasal endoscopy, saccharine time, and IL-8 levels in lavage fluid, and a correlation was noted improved outcome measures and low IgE levels.

However, there are also cases of sinusitis that are resistant to macrolide therapy (ME). It has been reported that the therapeutic efficacy of macrolides in improving the subjective symptoms decreases in patients with high eosinophil counts in the blood, nasal secretions and nasal mucosa, or high serum IgE levels [(14)]. In addition, it was reported that patients with a poor prognosis after endoscopic surgery for chronic sinusitis have a complication of bronchial asthma. On the other hand, it was

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reported that the efficacy of ME is not related to allergic symptoms or the severity of eosinophilic infiltration [3]. Moreover, it was reported that ME improves the signs and symptoms of asthma in bronchial asthma patients [15]. However, little studies have been carried out in regard to sinusitis that shows clear clinical resistance to ME, and there is a tendency for ME to be carried out without any clear purpose.

In the present study, we compared the clinical efficacy of ME as a function of the clinical findings (CT images, nasal findings and allergic factor) and subjective nasal symptoms. We thereby investigated the factors involved in resistance of chronic sinusitis to ME retrospectively.

MATERIALS AND METHODS

Subjects

The subjects were 68 patients with bilateral chronic sinusitis. For inclusion in the study, chronic sinusitis was defined as disease with persistent symptoms (nasal obstruction, nasal discharge, postnasal discharge, et al) for more than 12 weeks in association with opacification on computed tomography [16]. Patients with repeated acute rhinosinusitis were excluded. Chronic sinusitis was accompanied by nasal polyps in 39 of the patients (26 males, 13 females; 24~78 years of age, with a mean age of 53.7 years), but not in the remaining 29 patients (18 males, 11 females; 19~81 years of age, with a mean age of 48 years).

Clinical assessment

Chronic sinusitis was assessed on the basis of three factors: the CT images (radiographic findings), rhinoscopic (nasal) findings and allergic factors [17] (Figure 1).

The CT images were analyzed, and scores were assigned to the opacification observed in the frontal sinus, anterior and posterior ethmoidal sinuses, maxillary sinus and sphenoidal sinus. The scoring criteria were as follows: 0 points for a clear (no lesion) image, 1 point for a mild, focal lesion of the mucosa, 2 points for a moderate lesion and 3 points for a severe lesion. If there was a difference between the left and right sides, the points were totaled for the side showing the more severe lesions. A total score of 0~1 was R0, a score of 2~4 was R1, a score of 5~8 was R2 and a score of 9 or more was R3.

Radiographic findings (R)

Total scores of each sinus (anterior and posterior ethmoidal sinus, maxillary sinus, sphenoidal sinus and frontal sinus)

Clear:	**0**	Total scores of unilateral side ⟹	**R0 : 0,1**
Mild lesion:	**1**		**R1 : 2,3,4**
Moderate lesion:	**2**		**R2 : 5,6,7,8**
Severe lesion:	**3**		**R3 : more than 9**

Allergic examinations (A)

A0: no allergy

A1: nasal allergy

A2: asthma

Nasal findings (N)

N0 : no polyp

N1 : single polyp in the middle meatus or olfactory cleft

N2 : multiple polyps in the middle meatus and/or olfactory cleft, or polyps filling the nasal cavity

*** The side showing the more severe radiographic findings is estimated in the case of a difference in the severity between the right and left sides.**

Figure 1. The clinical images of the chronic sinusitis.

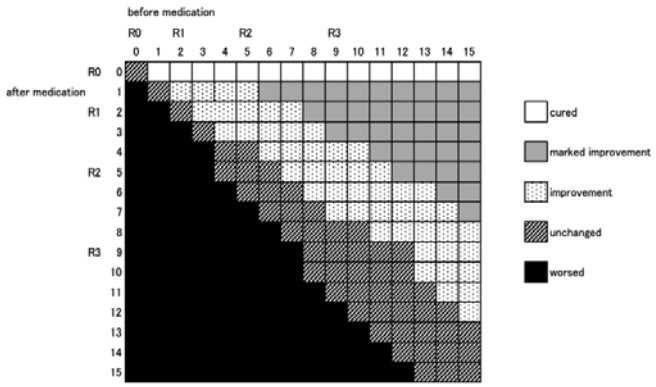

Figure 2. Five efficacy rates in CT images before and after medication.

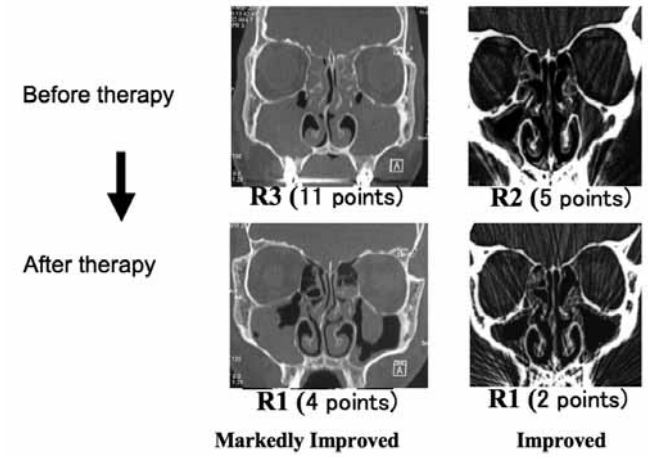

Figure 3. The examples of scoring in CT images before and after therapy.

The status in regard to nasal polyps was classified into three groups on the basis of the rhinoscopic findings. That is, the absence of polyps was classified as N0, while the presence of a single polyp in the middle meatus or olfactory cleft was classified as N1 and the presence of multiple polyps in the middle meatus or olfactory cleft was classified as N2. If there was a difference between the left and right sides, evaluation was performed of the side showing the more severe lesions in the image diagnosis.

For evaluation of allergic factors, a venous blood sample was taken to determine the eosinophil count (103/ml) and total serum IgE concentration. Also, the radioallergosorbent test (RAST) for common aeroallergens (house dust mites (Dermatophagoides pteronyssinus, Dermatophagoides farinae), Japanese cedar (Cryptomeria japonica, Chamaecyparis obtusa), dog hair, cat fur and a mixture of molds) was performed on all patients. The results were presented as RAST scores. The presence of atopy was estimated on the basis of a RAST score of 2 or higher or an IgE level higher than 250 UI/ml. The diagnosis

of asthma was made by a pulmonary physician following the guideline of the Japanese Society of Allergology, and the patients were then referred to the Otolaryngology Department. Based on the findings of allergic examinations, the patients were classified as A0 if they had no allergies, A1 if they had nasal allergy without asthma and A2 if they had bronchial asthma irrespective of nasal allergy.

The evaluation of the efficacy of the ME was performed on the basis of the change in the total score for each paranasal sinus in CT resulting from therapy, as shown in Figure 2. Five efficacy ratings were used: cured, markedly improved, improved, unchanged and worsened. Figure 3 shows a example of scores in CT images before and after therapy.

Nasal symptoms

The subjective symptoms were analysed based on the results of a questionnaire to the subjects with respect to nasal obstruction, nasal discharge, heavy-head feeling, and overall improvement. Each item was rated by a four-grade system (+++; ++; +; -). An improvement by at least two grades from pre-operative rating to post-operative rating (i.e., +++/+, +++/-. or ++/-) was defined as "good improvement"; an improvement by one grade (i.e., +++/++, ++/+, or +/-) was defined as "fair improvement"; no change in rating as "no change", and aggravation of existing symptom(s) or appearance of symptom(s) not seen before operation was defined as "aggravated" [18].

Low-dose, long-term macrolide therapy

Treatment with 14-membered ring macrolides was carried out as follows. Roxithromycin (RXM) was administered at 150 mg/day to 45 patients, while clarithromycin (CAM) was administered at 200 mg/day to 23 patients. The duration of administration was 8~20 weeks (mean: 13.8 weeks). The RXM group consisted of 28 patients who also had nasal polyps and 17 patients without polyps, while the CAM group included 11 patients with polyps and 12 without. The duration of administration was 8~20 weeks (mean: 14.2 weeks) for the patients with polyps and 8~20 weeks (mean: 12.1 weeks) for the patients without polyps. After polypectomy was performed on the patients with nasal polyps, RXM was again administered at 150 mg/day for 8~12 weeks (mean: 10.6 weeks). An acute exacerbation of the disease during the course of the therapy was found in 5 cases, and one case of those worsened twice. During the exacerbation the antibiotic was changed, and the macrolide was started again at the time when the acute aggravation was brought under control

Polypectomy

Surface anesthesia was achieved with 10% cocaine, 1:1000 epinephrine and 4% xylocaine. When the polyp was thought to be blocking the ostiomeatal complex (OMC), it was excised with cutting forceps or a Syaber System. Bleeding was stopped with gauze packing for two days.

Tissue preparation and staining

Samples were taken from the middle meatus and subjected to standard tissue processing with fixation for 24 hours in 10% buffered neutral formalin solution, followed by dehydration in graded alcohol solutions. Thereafter, they were embedded in paraffin blocks, serially cut into 3-μm-thick sections, and mounted on glass slides. The sections were stained with hematoxylin-eosin.

Measurements

Light microscopy was performed with a Nikon Microphoto-FXA microscope (Tokyo, Japan), examining at least two tissue sections for each sample. This used a 10x10 mm eyepiece graticule at a magnification of 200x (0.202 mm^2). The graticule was oriented along the epithelial basement membrane, which had to be undamaged for a length of at least 1 mm to be evaluable. The eosinophil cells and total inflammatory cells in the lamina propria were counted in three randomly selected fields, and a minimal area of 1 mm^2 was required for analysis.

Statistical analysis

Statistical significance was performed by the nonparametric Mann-Whitney U-test because the groups were unmatched. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed on a personal computer with the statistical package SPSS for Windows (Version 11.0, SPSS, Chicago, IL).

Informed consent

The study was performed with the informed consent of each of the patients.

RESULTS

Clinical findings of patients before ME

The following data were obtained regarding the patient background before the start of ME. The radiographic findings showed R1 in 11 patients, R2 in 26 patients and R3 in 31 patients. Similarly, classification on the basis of the allergic examinations showed 27 A0 patients, 36 A1 patients and 5 A2 patients, while the rhinoscopic examinations showed 29 N0 patients, 18 N1 patients and 21 N2 patients. The respective background classifications in the patient group having nasal polyps were 18 N1 patients and 21 N2 patients; 6 R1 patients, 17 R2 patients and 16 R3 patients; 21 A0 patients, 16 A1 patients and 2 A2 patients. Similarly, for the polyp-free patient group, the various classifications showed 5 R1 patients, 9 R2 patients and 15 R3 patients; 6 A0 patients, 20 A1 patients and 3 A2 patients. There was not different background between groups with and without polyp on performing EM.

Improvement of the subjective symptoms after ME

The degrees of improvement in the overall improvement show more than 70% regardless of complication with or without polyps, indicating the efficacy of ME. On the other hand, the

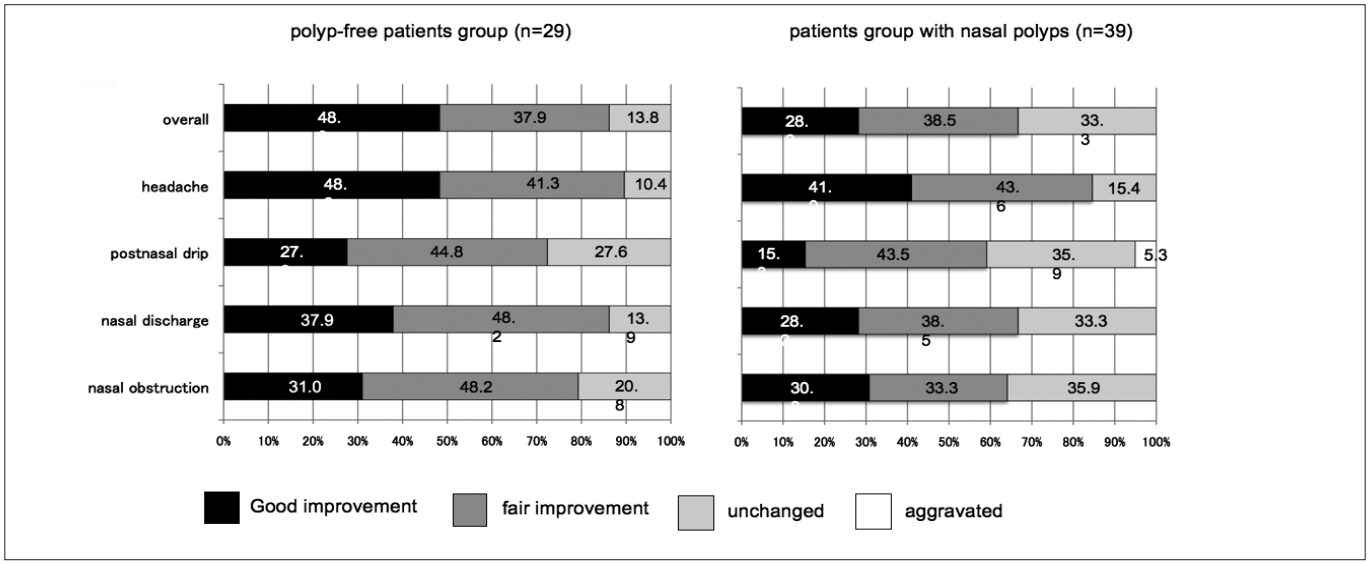

Figure 4. Rate improvement in subjective symtoms.

improvement of the nasal obstruction, nasal discharge and postnasal drip in the polyp-free patient group showed significantly better results than those in the patients group with nasal polyps ($p < 0.05$)(Figure 4).

Clinical efficacy after ME

The evaluation of the efficacy of the ME resulted in ratings of cured for 6 patients, markedly improved for 10 patients, improved for 32 patients and unchanged for 20 patients. No patients were rated as worsened. The improvement rate (i.e., improved or better) was 70.6% (48/68 patients).

In the patient group with nasal polyps, the 18 patients classified as N1 showed efficacy ratings of cured for one patient, markedly improved for 4 patients, improved for 8 patients and unchanged for 5 patients. When there were multiple polyps and the classification was N2 (21 patients), the efficacy rating was markedly improved for one patient, improved for 10 patients and unchanged for 10 patients. In the polyp-free patient group (29 patients), the efficacy rating was cured for 5 patients, markedly improved for 5 patients, improved for 14 patients and unchanged for 5 patients. Therefore, the efficacy of the macrolide therapy was significantly worse in the polyp group compared with the polyp-free group ($p < 0.05$). There was no statistically significant difference between N1 and N2.

The change in the rating of the radiographic findings (R) after the ME was investigated, and it was found that a change from R1 to R3 was accompanied by a significant worsening of the therapeutic efficacy ($p < 0.05$). Therefore, it was suggested that an effect of EM became worse as the CT image worsened.

On the other hand, comparison of the findings of allergic examinations (A) and the therapeutic efficacy found no correlation between the presence of nasal allergies and the efficacy, but there was a statistically significant increase in the percentage of asthma patients who became unchanged (Figure 5).

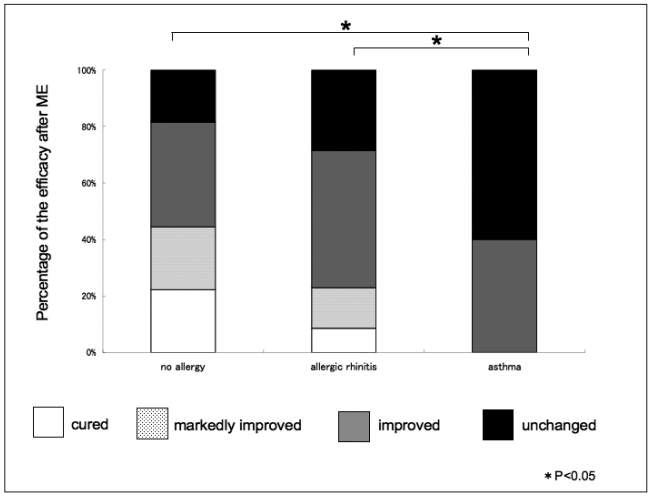

Figure 5. The relationship between the efficacy of the ME and allergic factors. The efficacy of asthma patients after ME was significant worse compared with those of alleric rhinitis and no allergy ($p < 0.05$).

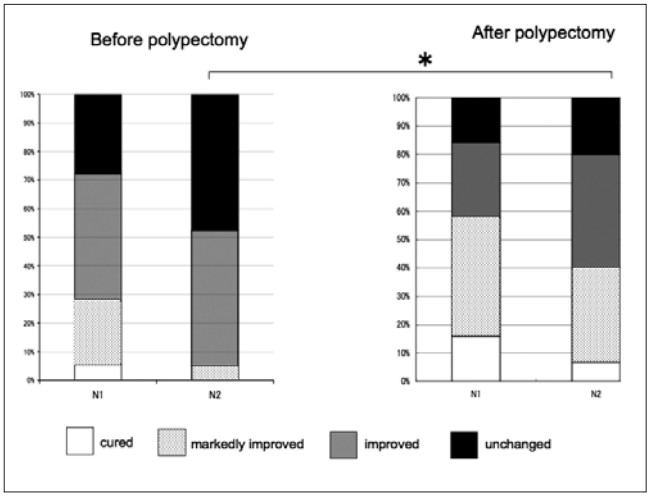

Figure 6. The efficacy of macrolide therapy before and after polypectomy. In the N2 group, the efficacy of the ME improved after polypectomy ($p < 0.05$), but not in the N1 group.

Clinical efficacy of ME after polypectomy

In five patients in the N1 polyp group the nasal polyp was found to have disappeared after the ME. In addition, six of the patients in the N2 polyp group improved to a rating of N1 after the therapy. Therefore, polypectomy was performed on 19 N1 patients and 15 N2 patients. The therapeutic efficacy of the ME after polypectomy was rated as cured in 3 patients, markedly improved in 8 patients, improved in 5 patients and unchanged in 3 patients in the N1 group. In the N2 group the efficacy was rated as cured in one patient, markedly improved in 5 patients, improved in 6 patients and unchanged in 3 patients. For the N2 group a statistically significant difference was found for the ME efficacy results between before and after polypectomy, but not for the N1 group (Figure 6). Therefore, it was suggested that the effect of ME for multiple polyps could be raised by resecting polyps.

Comparison between the infiltration of eosinophils in the polyps and the efficacy of ME

The percentage of eosinophils among the total inflammatory cells in the nasal polyp tissue was correlated with the efficacy of the ME after polypectomy. The results revealed a tendency for an increased eosinophil cell percentage in the order of cured, markedly improved, improved and unchanged, and the difference between markedly improved and unchanged was statistically significant (Figure 7). Sinusitis with infiltration of numerous eosinophils could not to be expected resulting from ME.

DISCUSSION

The conventional method for evaluating the therapeutic efficacy of macrolides in the treatment of chronic sinusitis has been staging on the basis of scores assigned to the CT image findings, anatomical variations, rhinoscopic findings and subjective symptoms [19]. However, more recently it has been postulated that morphological abnormalities of the OMC are not involved in cases of sinusitis with increased eosinophilic infiltration of the paranasal mucosa, and that the key factor is a high incidence of nasal polyposis, for which activated eosinophils serve as an index [20]. It has been reported that when endoscopic sinus surgery (ESS) is performed for sinusitis with severe eosinophilic infiltration, the postoperative course is poor in comparison with cases of sinusitis that are primarily due to OMC occlusion [21]. Therefore, in this study we evaluated the efficacy of ME in the treatment of chronic sinusitis accompanied by nasal polyps by taking into consideration the sinusitis features on the basis of CT findings, rhinoscopic findings, results of allergy tests and subjective nasal symptoms.

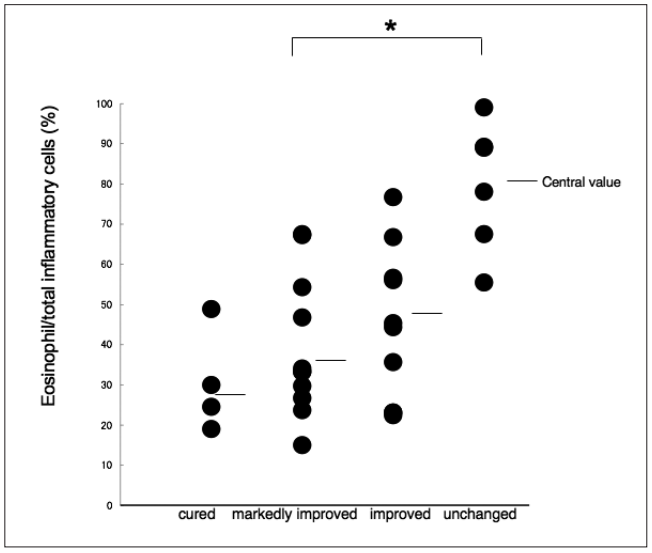

Figure 7. Comparison of the eosinophil cells in the total inflammatory cells with the efficacy of the ME after polypectomy. There was a tendency of the increase of the percentage of eosinophil cells in the order of cured, markedly improvement, improvement, unchanged.

We found that the efficacy of the ME for the chronic sinusitis was affected by the severity of the baseline CT findings and the presence/absence of polyps and asthma. It was reported that the macrolides were more effective in reducing the size of small polyps compared with large polyps [3]. We also found that ME eliminated polyps in the N1 group and reduced their size in the N2 group. However, the percentage of patients showing those effects was only 12.8% (5/39 patients). Accordingly, with the objective of improving the efficacy of the ME, we performed polypectomy to remove the polyps occluding the OMC and then continued the ME. The polypectomy could be performed on an outpatient basis, without requiring hospitalization, and it caused the patients little pain and was essentially noninvasive. This approach resulted in improved efficacy in the N1 patients, although it did not reach statistical significance, while in the N2 patients the efficacy was significantly improved compared with prior to the resection. Therefore, we conclude that the polypectomy, by eliminating the occlusion of the OMC that hindered aeration and drainage of the paranasal sinuses, was effective in promoting such reported actions of macrolides as enhancement of ciliary movement [7] and suppression of secretion of glycoconjugates (mucin) [8], and thereby promoted improvement in the chronic sinusitis.

In addition, there was a statistically significant increase in the percentage of eosinophils in the sampled polyp tissue of patients in whom the therapeutic efficacy of the macrolide therapy was poor. We can perhaps extrapolate that ME is unlikely to be effective in sinusitis patients with bronchial asthma, as a result of the concomitant eosinophilic infiltration.

However, the efficacy of the ME was evaluated as unchanged in 8.8% (6/68 patients) of the patients with no nasal polyps or after polypectomy. In such patients, ESS should be performed in order to open widely each of the paranasal sinuses and improve their aeration and drainage, and then it can be expected that the efficacy of subsequent ME will be enhanced [21].

CONCLUSIONS

1. The efficacy of ME was poor in relation to chronic sinusitis in patients with polyposis, CT scans indicating severe findings or concomitant bronchial asthma with eosinophil infiltrations.
2. Polypectomy resulted in statistically significant improvement in the efficacy of the ME

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