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Abstract

 We studied the clinical efficacy of roxithromycin (RXM) administered at the daily dosage of one tablet (150mg) for 3 months in 30 patients with chronic sinusitis. The effectiveness of this drug was evaluated on a four-point scale. Subjective and objective symptoms disappeared or decreased markedly, especially postnasal drip and nature of discharge in 80 percent or more of the patients. All symptoms significantly decreased ($P < 0.001$; headache $P < 0.05$), except for the sensation of foul odor. Symptoms improved even in those cases in which Haemophilus influenzae was detected. It is suggested that RXM produces some clinically beneficial effect through an immunological and or anti-inflammatory mechanisms in addition to its antibiotic effect.

KEYWORDS: roxithromycin, clinical evaluation, chronic sinusitis, long-term, low-dose administration

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Clinical Effect of Low-Dose, Long-Term Roxithromycin Chemotherapy in Patients with Chronic Sinusitis

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We studied the clinical efficacy of roxithromycin (RXM) administered at the daily dosage of one tablet (150mg) for 3 months in 30 patients with chronic sinusitis. The effectiveness of this drug was evaluated on a four-point scale. Subjective and objective symptoms disappeared or decreased markedly, especially postnasal drip and nature of discharge in 80 percent or more of the patients. All symptoms significantly decreased ($P < 0.001$; headache $P < 0.05$), except for the sensation of foul odor. Symptoms improved even in those cases in which *Haemophilus influenzae* was detected. It is suggested that RXM produces some clinically beneficial effect through an immunological and or anti-inflammatory mechanisms in addition to its antibiotic effect.

Key words: roxithromycin, clinical evaluation, chronic sinusitis, long-term, low-dose administration

Chronic sinusitis is one of the most common inflammatory diseases treated in otolaryngology-head and neck clinics. Generally the patients having severe mucosal hypertrophic lesions of the paranasal sinuses do not respond to antibiotic or other drug therapies. Sometimes these patients need to receive surgical treatment. In this study we examined the efficacy of a new medical option with long-term administration of roxithromysin (RXM) for this chronic sinusitis.

Recently, long-term administration of erythromycin (EM) has become the gold standard for the treatment of infected diffuse panbronchiolitis (DPB), a chronic complicated lung infection (1, 2). Long-term, low-dose EM therapy has also been reported to be effective for chronic sinusitis associated with DPB (3). RXM, an EM derivative, has also proven effective in patients with respiratory tract infection (4). Macrolides have several side effects apart from their anti-bacterial effects, for instance their effects on inflammatory airway cells play a significant role in improving local airway conditions associated with DPB. Since RXM has the characteristic bioavailability and pharmacokinetics (2, 5), we selected RXM for the treatment of chronic sinusitis.

Subjects and Methods

We studied 30 patients (14 men and 16 women, ranging 9 to 80 years old; mean 55.0 ± 20.9 years) diagnosed as having chronic sinusitis at the Department of Otolaryngology of the Hiroshima City Hospital between October 1991 and May 1994. Duration of illness ranged from 1 month to more than 40 years. Except for one patient who had undergone nasal polypectomy, none had received surgical treatment. Patients with small nasal polyps were included in this study, but patients with severe sinusitis and large polyps that filled the nasal cavity were excluded.

RXM was administered at a dose of one tablet (150 mg) daily for 3 months. Most of the patients took only RXM alone, but some were allowed to take other drugs concomitantly, such as anti-inflammatory enzymes, that were assumed not to affect the results of this study.

Roentgenologic examination of paranasal sinuses was performed before and after treatment with RXM and some patients received CT scans as well. Microorganisms in the sinuses were identified and tested for their sensitivity to several antibiotics before and after the administra-

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Table 1 Criteria for subjective symptoms

Degree of symptoms	Scores
Nasal obstruction	
Need for oral breathing	3
Frequently present	2
Not aware	1
No present	0
Rhinorrhea	
All day	3
Frequently	2
Two or three times a day	1
No nasal discharge	0
Postnasal drip	
Aware of it all day	3
Sometimes	2
Two or three times a day	1
Not aware	0
Sensation of foul odor	
Detectable by others	3
Present all the time	2
Sometimes present	1
Not present	0
Headache	
Always severe headache	3
Frequently present, but bearable	2
Sometimes aware	1
No headache	0

tion of RXM. Standard hematologic studies, as well as other clinical laboratory tests, including hepatic and renal function tests, were performed whenever possible. All patients provided their informed consent for participation in the study.

Criteria for the Efficacy of RXM

Subjective symptoms. Before and 1, 2 and 3 months after treatment, clinical effectiveness was evaluated (on a four-point scale from 0 to 3) using five parameters: nasal obstruction; amount of discharge, postnasal drip, sensation of foul odor, and headache (Table 1).

Improvement was assessed and given one of four grades by comparing scores before and 3 months after administration of RXM, in accordance with the criteria shown in Table 2.

Objective symptoms. Before and 1, 2 and 3 months after treatment, clinical efficacy was evaluated (on a four point scale from 0 to 3) for five parameters: hyperemia of mucous membrane, edema or swelling of the nasal mucous membrane, amount of discharge, nature of discharge, and amount of postnasal drip (Table 3).

Four grades of improvement were assigned (disappearance, improvement, no change, and exacerbation) by comparing scores before and 3 months after administration of RXM (Table 2).

Differences between pretreatment and post treatment scores for both subjective and objective symptoms were analyzed by the Wilcoxon signed-rank test.

Roentgenologic examination. Findings on x-ray films (areas of abnormal density) were classified on the following scale: severe = 3; moderate = 2; mild = 1; to none = 0. Improvement was judged according to the criteria listed in Table 2, based on conditions before and after the administration of RXM.

Table 2 Evaluation of amelioration of each symptom

Evaluation	Criteria Changes in scores (Before → After treatment)		
Disappearance	3 → 0	2 → 0	1 → 0
Improvement	3 → 2	3 → 1	2 → 1
No change	3 → 3	2 → 2	1 → 1
Exacerbation	0 → 1	0 → 2	0 → 3

Table 3 Criteria for objective symptoms

Degrees of symptoms	Scores
Hyperemia of mucous membrane	
High degree	3
Medium degree	2
Low degree	1
None	0
Edema or swelling of mucous membrane	
High degree	3
Medium degree	2
Low degree	1
None	0
Amount of discharge	
Large	3
Medium	2
Small	1
None	0
Nature of discharge	
Purulent	3
Mucopurulent	2
Mucous or serous	1
None	0
Amount of postnasal drip	
Large	3
Medium	2
Small	1
None	0

Results

Subjective symptoms. Fig. 1 shows the changes in subjective symptoms evaluated before and 1, 2 and 3 months after treatment with RXM. Scores for nasal obstruction, postnasal drip, and headache gradually decreased; the mean score for rhinorrhea was lowest after 2 months; that for a sensation of foul odor was lowest after 1 month. Three months after the start of RXM therapy, scores for all subjective symptoms, except for sensation of foul odor, were significantly lower than those before drug administration ($P < 0.05$–0.001).

As shown in Fig. 2, after administration of RXM for 3 months, subjective symptoms, especially postnasal drip and sensation of foul odor disappeared or decreased in about 80 percent or more of the patients. In half of the patients rhinorrhea disappeared.

Objective symptoms. Mean scores for all objective symptoms except postnasal drip gradually decreased throughout the treatment period (Fig. 3). This fact demonstrates that all objective symptoms significantly decreased compared with preadministration levels ($P < 0.001$).

Fig. 4 shows the decrease of objective symptoms in the patients. Among the 5 criteria, amount of discharge, nature of discharge and amount of postnasal drip, showed a high rate of improvement.

Roentgenologic findings. X-rays of the sinuses after 3 months of treatment with RXM showed "marked improvement" in 4 patients, "improvement" in 12, and "unchanged" in 11. No patients had the condition gotten worse.

Bacteriologic examination. In 29 of 30

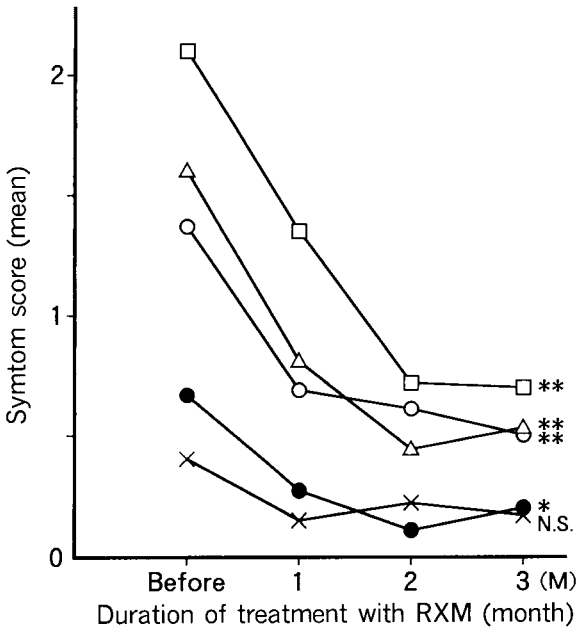

Fig. 1 Evaluation of changes in subjective symptoms (mean scores). (○), Nasal obstruction; (×), Sensation of foul odor; (△), Rhinorrhea; (●), Headache; (□), Postnasal drip; RXM: roxithromycin. RXM: Roxithromycin.

$*P < 0.05$; $**P < 0.001$.

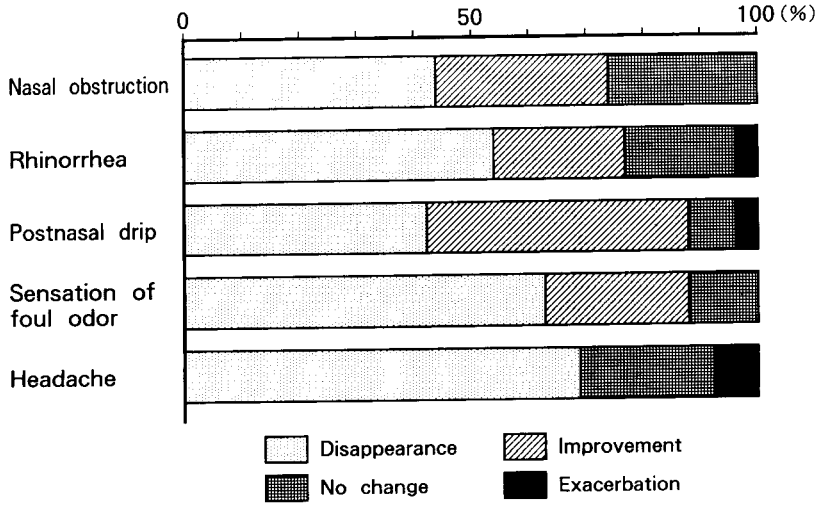

Fig. 2 Evaluation of amelioration of subjective symptoms according to four grades (disappearance, improvement, no change, and exacerbation) by comparing scores before and 3 months after administration of roxithromycin.

patients, the organisms isolated from nasal discharge before administration of RXM were *Staphylococcus epidermidis* (7 cases), *Staphylococcus aureus* (8 cases), *α-hemolytic streptococci* (5 cases), *Haemophilus influenzae* (4 cases), *Streptococcus pneumoniae* (2 cases), *Branhamella catarrhalis* (1 case), *Pseudomonas aeruginosa* (1 case) and Neisseria (1 case). Since these patients indicated few rhinorrhea after RXM therapy, we could not measure the bacteria in the nasal smear.

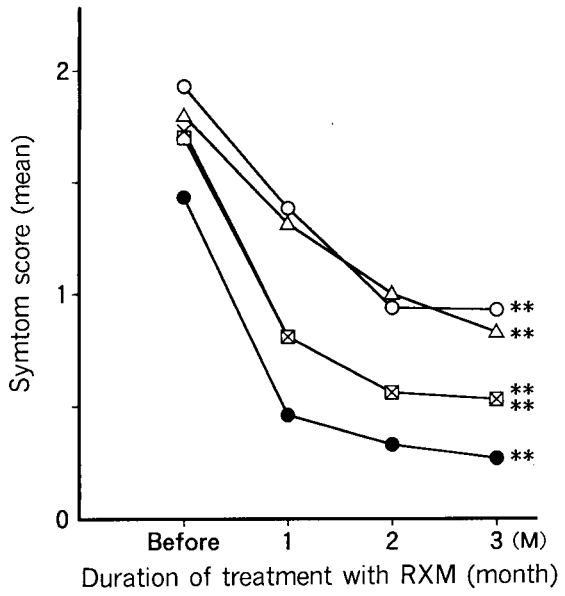

Fig. 3 Evaluation of changes in objective symptoms (mean scores). (○), Hyperemia of mucous membrane; (×), Nature of discharge; (△), Edema or swelling of mucous membrane; (●), Amount of Postnasal drip; (□), Amount of discharge. RXM: See Fig. 1.
**; $P < 0.001$

Discussion

Chronic sinusitis is a problematic condition caused by several different mechanisms including allergy, mucociliary dysfunction, impaired drainage of the sinus due to mucosal edema and/or fibrosis, and persistent or recurrent bacterial infection. Conventional medical management with antibiotics, mucolyticus and topical usage of steroid and anti-inflammatory drugs is not effective in a significant number of patients, and reported effectiveness rates vary from 40 to 80 % (6). In the present study, using RXM for 3 months, the subjective symptoms, postnasal drip and sensation of foul odor, and objective symptoms, nature of discharge and amount of postnasal drip, disappeared or decreased in more than 80 percent of the cases. All symptoms, except for a sensation of foul odor, were significantly relieved. Although RXM is basically ineffective against gram-negative bacteria, symptoms decreased even in those cases in which *Haemophilus influenzae* was detected. Consequently, we conclude that long-term RXM therapy provides a good medical option for treating patients with chronic sinusitis.

Macrolides, especially 14-membered macrolides such as EM and RXM, have several side effects apart from their anti-bacterial effects, including an inhibitory effect on airway mucous secretion, and activating effect on phagocytic function of macrophages, and an inhibitory effect on the chemotactic activity of polymorphonuclear leukocytes (2, 5). Moreover, they have an inhibitory effect on the

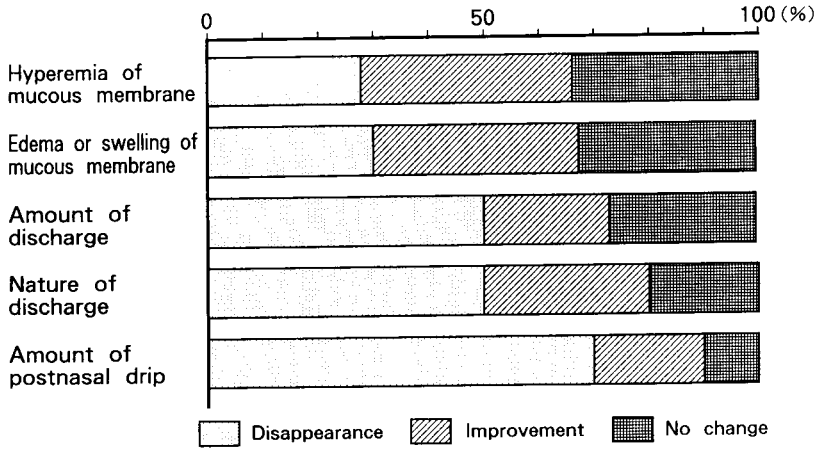

Fig. 4 Evaluation of amelioration of objective symptoms according to four grades (disappearance, improvement, no change, and exacerbation) by comparing scores before and 3 months after administration of roxithromycin.

production of bacterial virulence factors, including bacterial exopolysaccharide. EM also has immunoenhancing effects, such as stimulation of the production of specific antibodies to organisms (7) and the acceleration of the migration and phagocytic activity of neutrophils (8). It is possible that this kind of biological response modifier improves and corrects local conditions associated with chronic sinusitis together with its antibiotic effect. Thus, it appears that this treatment may have the effect of ending a vicious circle. Namely, that in which impaired local conditions account for persistent or recurrent infection which in turn re-impairs the local conditions.

Although a further study, possibly a prospective comparative study, is still needed before prescribing routine use, RXM therapy is effective in selected patients and might be recommended for use in patients awaiting surgical interventions.

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