

## Effects of Long-Term Low-Dose Macrolide Administration on Neutrophil Recruitment and IL-8 in the Nasal Discharge of Chronic Sinusitis Patients

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SUZUKI, H., SHIMOMURA, A., IKEDA, K., OSHIMA, T. and TAKASAKA, T. *Effects of Long-Term Low-Dose Macrolide Administration on Neutrophil Recruitment and IL-8 in the Nasal Discharge of Chronic Sinusitis Patients.* Tohoku J. Exp. Med., 1997, **182** (2), 115-124 — Effects of long-term low-dose macrolide administration were studied in patients with chronic sinusitis. Twelve patients with non-allergic chronic sinusitis were orally given 150 mg roxithromycin once a day without other treatments. The patients underwent computed tomography before and after the treatment, and paranasal sinus aeration was analyzed quantitatively. The number of neutrophils in the nasal smear was semiquantitatively assessed on a grading scale, and the IL-8 concentration in the nasal discharge was measured by enzyme immunoassay. The aeration of all four sinuses significantly improved, and recruited neutrophils and the IL-8 level in the nasal discharge were simultaneously reduced after the treatment. These findings suggest that long-term low-dose roxithromycin administration inhibits the positive feedback mechanism of neutrophil recruitment and IL-8 production by the recruited neutrophils, which is considered to be an essential cause of the prolongation of sinusitis. ——— macrolide; long-term low-dose administration; chronic sinusitis; IL-8; neutrophil  
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Chronic sinusitis is characterized by purulent paranasal sinus effusion and nasal discharge with numerous emigrated neutrophils. This disease is frequently associated with lower respiratory tract diseases including diffuse panbronchiolitis. This association is referred to as sinobronchial syndrome (Sugiyama 1993). Both diseases have some characteristics in common. Both of them affect the respiratory tract, and manifest mucosal thickening (Mukae et al. 1993; Sugiyama 1993) and persistent purulent secretion with marked neutrophil emigration (Kadota et al. 1993; Koga 1993). Moreover, in both diseases, a high level of interleukin-8 (IL-8) is detected in the secretions (Koga 1993; Suzuki et al. 1996). These

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observations suggest that chronic sinusitis and diffuse panbronchiolitis may share the same mechanism of neutrophil recruitment. In recent years, long-term low-dose macrolide administration, which was introduced for the treatment of diffuse panbronchiolitis (Kudoh et al. 1987), has been proved to be an effective treatment of sinobronchial syndrome (Iino et al. 1992, 1993). This therapy is, accordingly, very likely to be effective against simple chronic sinusitis. In the present study, the effects of long-term low-dose macrolide treatment on the improvement of paranasal sinus aeration, neutrophil recruitment and the IL-8 level in the nasal discharge were examined in non-allergic chronic sinusitis patients.

## SUBJECTS AND METHODS

### *Patients*

Twelve non-allergic chronic sinusitis patients were studied. A diagnosis of chronic sinusitis was made according to the following criteria; (i) sinus-related clinical symptoms, (ii) purulent/mucopurulent secretion and/or polyps in rhinoscopic examination, (iii) opacification of paranasal sinuses in computed tomography (CT) scan, and (iv) predominant neutrophils without eosinophils in nasal smear. All the patients suffered from the disease for 6 months or more, and had been resistant to other conservative treatments. None had manifest symptoms of lower respiratory tract inflammations or allergic rhinitis. Patients with allergic sinusitis were not included; i.e., patients with more than 250 units/ml of total serum IgE or positive radioallergosorbent tests (RAST) for specific serum IgE were considered to be in an atopic state, and were excluded from the study. House dust mite, Japanese cedar pollen, orchard-grass pollen, short ragweed pollen and *Candida albicans* were examined as allergic antigens in RAST, which were evaluated to be positive when at least one item was present. The subjects consisted of 8 males and 4 females, ranging in age from 16 to 73 years with the average age of 53.5 years.

### *Macrolide administration*

The patients were kept free of antibiotics, antihistamines, anti-allergic medicine and nasal corticosteroids for at least one week before starting macrolide administration. They were orally given 150 mg roxithromycin, a 14-membered ring macrolide, once a day without other concurrent treatments.

### *Quantitative analysis of paranasal sinus aeration*

The patients underwent CT of paranasal sinuses before and at the end of the treatment. Serial axial-plane images were taken every 5 mm. In order to quantitatively evaluate sinus aeration, the areas of paranasal sinuses and aerated regions within the sinuses were measured using the public domain NIH Image program (written by Wayne Rasband at the U.S. National Institute of Health and available from the Internet by anonymous ftp from zippy.nimh.nih.gov or on

floppy disk from NTIS, 5285 Port Royal Rd., Springfield, VA 22161, part number PB93-504868) on a Macintosh Quadra 650 computer. Then, for each patient, the sinus areas and the aerated areas within the sinus from each of the serial CT images were summed up, and %aeration was calculated using the equation,

$$\% \text{aeration} = (\text{sum of aerated areas within the sinus} / \text{total sinus area}) \times 100.$$

#### *Estimation of neutrophils in nasal smear*

Nasal discharge was collected by a cotton stick, spread on a poly-L-lysine-coated slide glass and dried in air. The nasal smear was then stained with Hansel solution (Torii Co., Tokyo). The number of neutrophils in the specimen was semiquantitatively assessed on a grading scale; i.e., (-) = no neutrophils, ( $\pm$ ) = less than 10 neutrophils in the whole specimen, (+) = neutrophils sparsely scattered in the field, (++) = between (+) and (+++), and (+++) = neutrophils forming clusters.

#### *Measurement of IL-8 in nasal discharge*

Nasal discharge was collected by suction and diluted 5–10 times with saline. After thorough mixing, the sample was centrifuged at  $1000 \times g$  for 5 minutes, and the supernatant was collected and stored at  $-20^{\circ}\text{C}$  until measurement. The IL-8 concentration in the supernatant was measured by enzyme immunoassay using a Quantikine ELISA kit (R & D systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

#### *Statistics*

Data values were expressed as mean  $\pm$  s.e.m. The type of statistical test is indicated in Results. Differences were considered to be significant when  $p$  value was  $< 0.05$ .

## RESULTS

#### *Paranasal sinus aeration*

Quantitative evaluation of the changes of paranasal sinus aeration was performed in 10 cases. The period of roxithromycin administration varied from 4 to 11 months with the average period being 5.1 months. Fig. 1 shows CT images of a 55-year-old male before and after 11 months of roxithromycin administration. %Aeration of the maxillary sinus was 7.1% before, and increased to 47.9% at the end of the treatment. The results are summarized in Fig. 2. %Aeration significantly increased in the maxillary sinus ( $p < 0.01$ ), ethmoid sinus ( $p < 0.01$ ), sphenoid sinus ( $p < 0.05$ ) and frontal sinus ( $p < 0.01$ ) (two-tailed paired  $t$ -test).

#### *Neutrophils and the IL-8 level in nasal discharge*

Inflammatory cells in the nasal smear were mostly neutrophils ( $\geq 95\%$ ) with

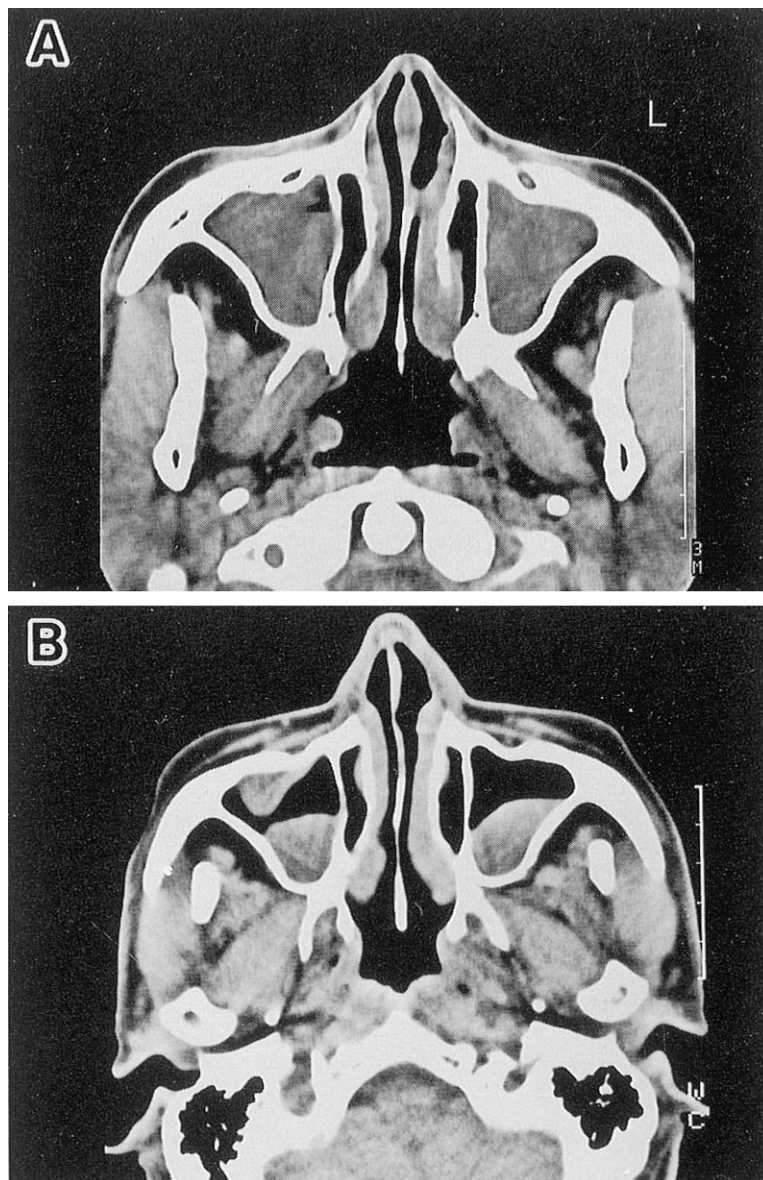


Fig. 1. Paranasal sinus CT images of a 55-year-old male before and after roxithromycin administration. The patient was orally given 150 mg roxithromycin once a day without other treatments. %Aeration of the maxillary sinus was 7.1% before the treatment (A), and increased to 47.9% at the end of 11 months of administration (B).

a small number of mononuclear cells such as lymphocytes and monocyte/macrophages, and no eosinophils before roxithromycin administration. The neutrophil score decreased in 7 cases out of 12 (58%) after 2 months and in 6 cases out of 10 (60%) after 3 months (Fig. 3). The decrease was statistically significant after both 2 months and 3 months (Wilcoxon signed rank test,  $p < 0.05$ ). The treatment brought about no significant change in other inflammatory cell populations.

The IL-8 level in the nasal discharge was  $14.3 \pm 3.8$  nM before the treatment,  $12.8 \pm 5.4$  nM after 2 months and  $5.3 \pm 1.7$  nM after 3 months (Fig. 4). The IL-8 level was lowered in 9 cases out of 12 (75%) after 2 months and in 9 cases out of 10 after 3 months (90%). There was a significant decrease after 3 months of administration (two-tailed paired  $t$ -test,  $p < 0.01$ ). Moreover, correlation between



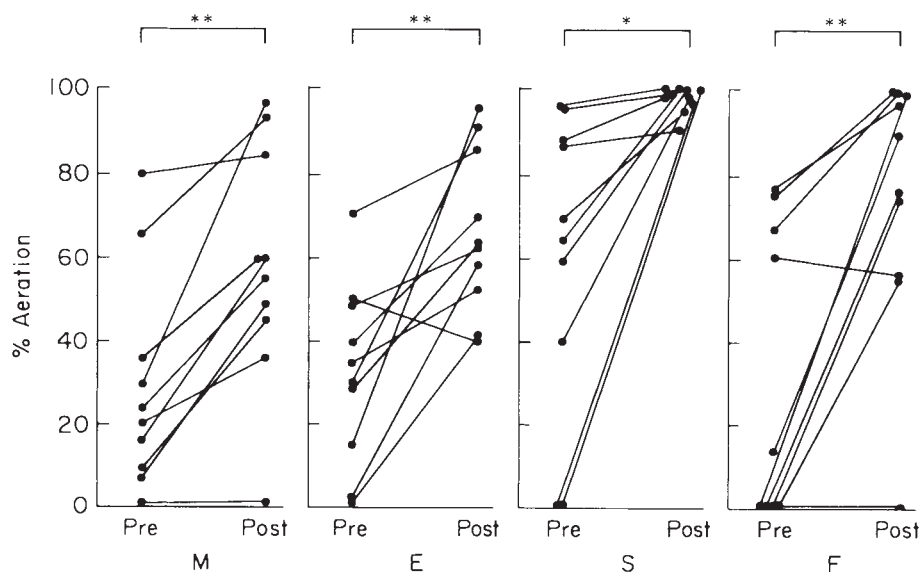


Fig. 2. Effect of roxithromycin administration on paranasal sinus aeration. Non-allergic chronic sinusitis patients were orally given 150 mg roxithromycin once a day without other treatments. The patients underwent computed tomography (CT) of paranasal sinuses before and at the end of the treatment. The period of administration varied from 4 to 11 months with the average period being 5.1 months. Serial axial-plane images were taken every 5 mm, and the areas of paranasal sinuses and aerated regions within the sinuses were measured using the public domain NIH Image program. Then, the areas from each of the serial CT images were summed up, and %aeration was calculated as follows;

$$\% \text{aeration} = (\text{sum of aerated areas within the sinus} / \text{total sinus area}) \times 100.$$

M, maxillary sinus; E, ethmoid sinus; S, sphenoid sinus; F, frontal sinus.

\* $p < 0.05$ , \*\* $p < 0.01$  (paired  $t$ -test).

the neutrophil score of the nasal smear and the IL-8 level in the nasal discharge was statistically significant with a Spearman rank correlation coefficient of 0.664 ( $n = 26$ ,  $p < 0.001$ , Fig. 5).

## DISCUSSION

A number of authors have so far documented the efficacy of long-term low-dose macrolide administration for the treatment of diffuse panbronchiolitis (Kudoh et al. 1987; Nagai et al. 1991; Ichikawa et al. 1992; Akira et al. 1993; Kadota et al. 1993; Mukae et al. 1993; Oda et al. 1994, 1995; Matsumoto 1995; Shirai et al. 1995) and sinobronchial syndrome (Iino et al. 1992, 1993). In addition, based on the measurement of sinus aeration in CT scanned images (Fig. 1), the present study showed that this therapy is also effective against simple chronic sinusitis. However, the mechanism of the action of the drug is not fully understood. Several lines of evidence indicate that this drug does not function primarily as a bactericide in this therapy. Nagai et al. (1991) observed that the maximum serum and sputum levels of erythromycin during low-dose therapy were below the minimum inhibitory concentrations of clinically pathogenic bacteria. Moreover, macrolide-resistant bacteria such as *Pseudomonas aeruginosa* are fre-

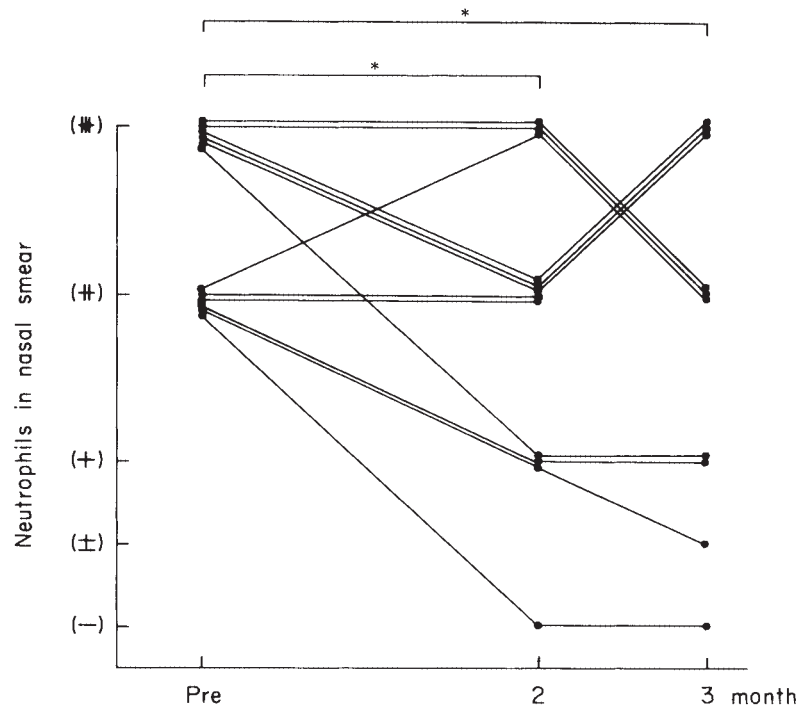


Fig. 3. Effect of roxithromycin administration on nasal smear neutrophils of chronic sinusitis patients. The number of neutrophils in the nasal smear was assessed according to a grading scale; i.e., (-)=no neutrophils, (±)=less than 10 neutrophils in the entire specimen, (+)=neutrophils sparsely scattered in the field, (++)=between (+) and (+++), and (+++)=neutrophils forming clusters. \* $p < 0.05$  (Wilcoxon signed rank test).

quently detected in the inflammatory site of diffuse panbronchiolitis patients (Nagai et al. 1991; Kadota et al. 1993; Matsumoto 1995). The ineffectiveness of a 16-membered ring macrolide, josamycin, in contrast to the efficacy of 14-membered ring macrolides (Shirai et al. 1995) again suggests that the mechanism of macrolide therapy in diffuse panbronchiolitis is not yet understood.

Several investigators have reported a variety of effects of macrolide antibiotics on immunocompetent cells, inflammatory cells and airway epithelial cells. It has been shown in in vitro studies that these drugs modulate proliferation, differentiation, cytokine production and phagocytosis of monocytes and macrophages (Takeshita et al. 1989; Iino et al. 1992; Kita et al. 1993; Keicho et al. 1994; Pierce et al. 1995; Yoshimura et al. 1995) improves ciliary movement of airway epithelium (Takeyama et al. 1993), inhibits ion and mucus secretion from epithelial cells (Goswami et al. 1982; Ikeda et al. 1995), and inhibits bacterial adhesion to nasal epithelium (Ishida et al. 1995). Furthermore, it has been reported that the number of neutrophils, neutrophil chemotactic activity and the levels of IL-8 and LTB<sub>4</sub> in the bronchoalveolar lavage fluid were reduced after the administration of erythromycin in diffuse panbronchiolitis patients (Kadota et al. 1993; Oda et al. 1994, 1995; Oishi et al. 1994). It is also known that erythromycin inhibits the motile ability of neutrophils (Nelson et al. 1987; Torre et al. 1991; Kadota et al. 1993; Shirai et al. 1995). On the basis of these observations, Kadota et al.

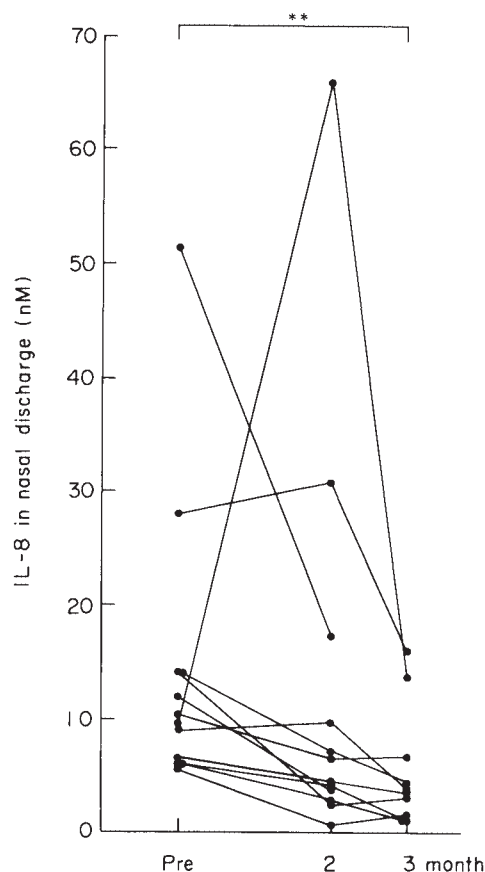


Fig. 4. Effect of roxithromycin administration on the IL-8 level in the nasal discharge of chronic sinusitis patients. Nasal discharge was collected by suction and diluted 5–10 times with saline. After thorough mixing, the sample was centrifuged at  $1,000 \times g$  for 5 minutes, and the supernatant was collected and stored at  $-20^{\circ}\text{C}$  until measurement. The IL-8 concentration in the supernatant was measured by enzyme immunoassay using a Quantikine ELISA kit (R & D systems) according to the manufacturer's instructions.  $**p < 0.01$  (paired  $t$ -test).

(1993) speculated that macrolide treatment reduces the intrapulmonary neutrophil chemotactic gradient and restrains neutrophils from responding to chemotactic factors, eventually suppressing the migration of neutrophils to inflammatory sites.

Recent advances in sinusitis research have revealed that IL-8 plays an essential role in the neutrophil recruitment in chronic sinusitis (Takeuchi et al. 1995; Suzuki et al. 1996). Additionally, the authors previously showed that the emigrated neutrophils produce IL-8, which elicits further neutrophil accumulation, constituting a positive feedback mechanism to prolong the inflammation in situ (Suzuki et al. 1996). Therefore, in the present study, we focused on the effect of a macrolide antibiotic on neutrophil recruitment and the IL-8 level in the nasal discharge of non-allergic chronic sinusitis patients. Both the number of recruited neutrophils and the IL-8 level were reduced after long-term low-dose roxithromycin administration (Figs. 3 and 4). Moreover, there was significant correlation between the two parameters (Fig. 5). These findings suggest that roxithromycin suppresses IL-8 secretion from various cells in inflammatory sites such as

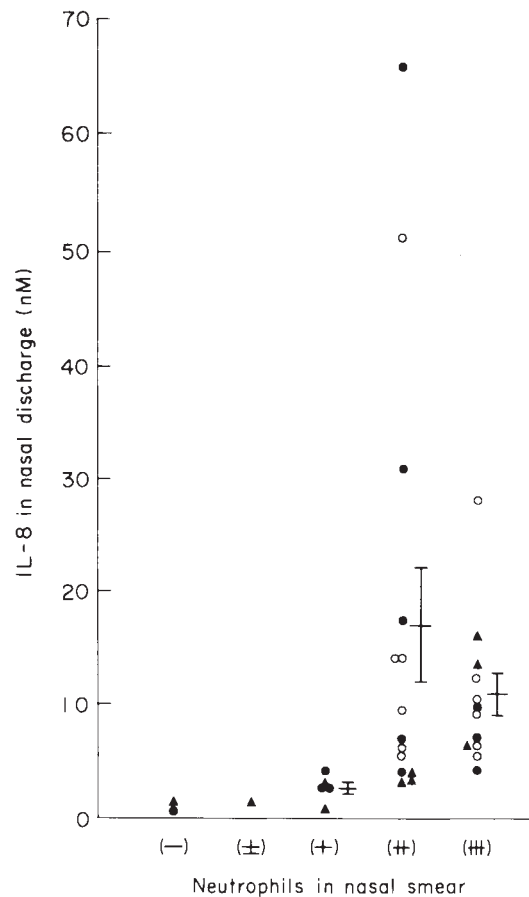


Fig. 5. Correlation between the IL-8 level in the nasal discharge and the number of neutrophils in nasal smear in the same grading as in Fig. 3.

Open circles, closed circles and closed triangles represent the data of before administration, after 2 months and after 3 months of administration, respectively. The correlation was statistically significant with a Spearman rank correlation coefficient of 0.664 ( $p < 0.001$ ).

nasal gland duct cells, epithelial cells and recruited neutrophils, and consequently inhibits the positive feedback mechanism of neutrophil recruitment and IL-8 production.

Because chronic sinusitis itself does not have lethal prognosis, clinical use of anti-cytokine antibody and anti-sense oligonucleotide, which may bring about severe side effects, is inappropriate for the treatment of this disease. However, it has been pointed out that chronic nasal and paranasal sinus inflammations might provoke and aggravate lower respiratory diseases including bronchial asthma at a higher incidence than previously anticipated (Irvin 1992; Brugman et al. 1993; Bucca et al. 1995a, b). A safe and reliable remedy is, accordingly, needed to cure chronic sinusitis patients to prevent their quality of life from worsening. The present study demonstrated that long-term low-dose macrolide administration is clinically effective against chronic sinusitis, and probably involves the inhibition of the positive feedback of neutrophil recruitment and IL-8 production. The mode of action of macrolide antibiotics remains to be elucidated, and this may lead to the development of a new cytokine therapy for chronic sinusitis as well as



diffuse panbronchiolitis.

In conclusion, effects of long-term low-dose administration of roxithromycin, a 14-membered ring macrolide antibiotic, were studied in non-allergic chronic sinusitis patients. Aeration of paranasal sinuses evaluated by CT scan was significantly improved, and neutrophils and the IL-8 level in the nasal discharge were simultaneously reduced after the treatment. These findings suggest that long-term low-dose roxithromycin administration inhibits the positive feedback of neutrophil recruitment and IL-8 production by the recruited neutrophils, which is an essential mechanism in the prolongation of sinus inflammation.

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