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A Double-Blind, Randomized, Placebo-Controlled Trial of Macrolide in the Treatment of Chronic Rhinosinusitis

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Objectives: **The antiinflammatory effect of macrolide antibiotics has been well-established, as has their role in the treatment of certain disorders of chronic airway inflammation. Several studies have suggested that long-term, low-dose macrolides may be efficacious in the treatment of chronic rhinosinusitis; however, these studies have lacked a control group. To date, this effect has not been tested in a randomized, placebo-controlled study.** ***Method:*** **The authors conducted a double-blind, randomized, placebo-controlled clinical trial on 64 patients with chronic rhinosinusitis. Subjects received either 150 mg roxithromycin daily for 3 months or placebo. Outcome measures included the Sinonasal Outcome Test-20 (SNOT-20), measurements of peak nasal inspiratory flow, saccharine transit time, olfactory function, nasal endoscopic scoring, and nasal lavage assays for interleukin-8, fucose, and a2-macroglobulin.** ***Results:*** **There were statistically significant improvements in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid ($P < .05$) in the macrolide group. A correlation was noted between improved outcome measures and low IgE levels. No significant improvements were noted for olfactory function, peak nasal inspiratory flow, or lavage levels for fucose and a2-macroglobulin. No improvement in any outcome was noted in the placebo-treated patients.** ***Conclusion:*** **These findings suggest that macrolides may have a beneficial role in the treatment of chronic rhinosinusitis, particularly in patients with low levels of IgE, and supports the in vitro evidence of their antiinflammatory activity. Additional studies are required to assess their place in clinical practice.** ***Key Words:*** **Macrolide, chronic rhinosinusitis, placebo-controlled,**

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INTRODUCTION

In recent years, considerable evidence has emerged to suggest that macrolide antibiotics have an antiinflammatory effect in addition to their well-established antibiotic effect. Macrolides have been shown to inhibit cytokine production,[1] alter bacterial biofilm formation,[2] increase inflammatory cell apoptosis,[3] and inhibit the activation of the key proinflammatory transcription factor nuclear factor-κB.[4] This antiinflammatory activity has been used to treat disorders of chronic airway inflammation such as diffuse panbronchiolitis, cystic fibrosis, and asthma.

A number of studies have examined the efficacy of macrolides in the treatment of chronic rhinosinusitis and have suggested a clinical benefit.[5–7] These studies have contained small patient numbers and have lacked a placebo-controlled group. The objective of this study was to examine the use of long-term, low-dose macrolides in the treatment of chronic rhinosinusitis in a double-blind, randomized, placebo-controlled trial. A variety of subjective and objective outcome measures have been used. In addition, we have performed a subgroup analysis comparing the response to treatment of patients with low compared with high levels of serum immunoglobulin E (IgE).

MATERIALS AND METHODS

Subjects

Patients were recruited from the ear, nose and throat departments of the Royal Brisbane Hospital and the Gold Coast Hospital over an 18-month period. Patients were included if they were aged greater than 18 years with a history consistent with the diagnosis of chronic rhinosinusitis as outlined by the Rhinosinusitis Task Force.[8] A computed tomography (CT) scan was performed to confirm the diagnosis and was scored using the Lund-Mackay CT scoring system.[9] Patients were excluded if they had a history of cystic fibrosis, primary ciliary dyskinesia, immune deficiency, allergic fungal sinusitis, nasal polyposis, and impairment of liver or renal function. Pregnant and breastfeeding women were excluded as were those taking medications with a known adverse interaction with macrolides or with a history of

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macrolide hypersensitivity. Patients were ineligible for inclusion if they had used topical or systemic corticosteroids within 4 weeks of entering the study. The study protocol was approved by the ethics committees of the Royal Brisbane and Gold Coast Hospitals and Griffith University.

Experimental Procedures

After recruitment into the study, subjects were randomized by the pharmacy department, using a random number table, to receive 150 mg roxithromycin daily for 3 months or placebo. Patients and investigators were kept blinded to the randomization until the completion of the study. At the beginning and end of treatment, patients completed the Sinonasal Outcome Test-20 (SNOT-20) questionnaire and had measures of peak nasal inspiratory flow, saccharine transit time, nasal endoscopic scoring, olfactory function, and nasal lavage for IL-8, a2-macroglobulin, and fucose. In addition, the SNOT-20 questionnaire was completed at the midpoint of the treatment period and 3 months after the completion of treatment.

Microbiology and Blood Testing

Microbiologic swabs were obtained and analyzed from the middle meatus of patients pre- and posttreatment. Blood testing at enrollment in the study included serum eosinophil count, radioallergosorbent test (RAST), and serum immunoglobulin E.

Subjective Measures

Sinonasal Outcome Test-20. Patients completed the SNOT-20 questionnaire at their enrollment into the study, after 6 weeks of treatment, posttreatment, and 12 weeks posttreatment. The SNOT-20 is a validated, rhinosinusitis-specific quality-of-life instrument in which patients are asked to answer 20 questions regarding their nasal symptoms and quality of life.[10]

Patient Response Scale. At the conclusion of the 3-month treatment period, patients were asked to give an overall indication of their response to treatment on a linear rating scale (1, completely improved; 2, much improved; 3, slightly improved; 4, not improved; 5, slightly worse; 6, much worse).

Objective Measures

Peak Nasal Inspiratory Flow. Peak nasal inspiratory flow was measured at the pre- and posttreatment visits (In-Check; Clement Clark Limited, Harlow, Essex, U.K.). Patients performed three inhalations and the mean value was recorded.

Saccharine Transit Time. A particle of saccharine was placed unilaterally on the lateral nasal wall, 1 cm posterior to the anterior end of the inferior turbinate. The time was recorded from the placement of the particle to the first perception of the saccharine taste.

Nasal Endoscopy. The patient's nasal cavities were examined with a nasal endoscope at the pre- and posttreatment visits. All examinations were performed by the primary author. Endoscopic scoring was carried out according to a template that graded swelling (0, no swelling; 1, mild swelling; 2, severe swelling), mucosal color (0, pale; 1, red), polyps in the middle meatus (0, absent; 1, present), and nasal secretions (0, normal; 1, watery; 2, mucoid; 3, purulent).

Olfactory Function. Olfactory testing was performed using the Sniffin' sticks olfactory function test (Burghardt, Wedel, Germany). Scores were obtained for odor detection threshold, odor discrimination, and odor identification and were added to give a possible maximum score of 48.[11,12]

Nasal Lavage. Nasal lavages were performed for 30 seconds using a compressible plastic nasal pool device filled with 10 mL of isotonic saline. The lavage fluid samples were processed by ultrasonication for 15 minutes and then assays were performed for interleukin-8 (IL-8), a2-macroglobulin, and fucose. IL-8 was measured using a commercially available enzyme linked immunosorbent assay (R&D Systems, U.K.). α2-macroglobulin and fucose levels were determined using a previously described technique.[13]

Statistical Methods

Statistical analysis was performed using the GraphPad Prism 4 software package (GraphPad, SanDiego, CA). A power analysis predicted sample sizes of 25 in each group would be required to achieve power of 80% at the 1% level of significance. The primary end point was the patient response scale. Data are expressed as mean $\pm$ standard error of mean. An intention-to-treat analysis was used. The Mann-Whitney *U* test was applied to the patient response scale data. The Wilcoxon signed rank test was applied to the remaining data. P values $< .05$ were considered significant.

RESULTS

Subjects

Sixty-four subjects were recruited into the study and were randomized to receive roxithromycin (n = 29) or placebo (n = 35). Three subjects withdrew from the placebo group (one subject was lost to follow up, one developed a rash, and one developed abdominal pain during placebo treatment). Two subjects withdrew from the roxithromycin group (one subject developed nausea and vomiting on beginning treatment and one was lost to follow up). Three subjects did not complete the 12-week posttreatment SNOT-20 survey (one subject in the roxithromycin group and two in the placebo group).

No significant differences were identified between the placebo and roxithromycin groups in terms of age, sex, IgE, CT scores, or baseline values of SNOT-20 scores, peak nasal inspiratory flow, saccharine transit time, nasal endoscopy, olfactory function scores, and lavage data.

Nasal swabs were taken for microbiologic examination before and after the completion of treatment. In the 29 roxithromycin-treated patients, there were 12 positive cultures at the beginning of treatment (*Staphylococcus aureus* n = 4, *Haemophilus influenzae* n = 1, *Pseudomonas aeruginosa* n = 3, *Streptococcus pneumoniae* n = 4). After treatment in these patients, there were nine positive cultures (*S. aureus* n = 5, *P. aeruginosa* n = 2, *S. pneumoniae* n = 2). No macrolide-resistant organisms were noted to develop.

Roxithromycin versus Placebo

Patient Response Scale. Patients completed the linear rating scale at the posttreatment visit. A statistically significant difference was identified between the roxithromycin (3.11 $\pm$ 0.17; range, 2–5) and placebo groups (3.84 $\pm$ 0.12; range, 2–5) ($P < .01$).

Pre-versus Posttreatment Outcome Measures

The pre- and posttreatment outcome measures for the roxithromycin-treated patients and placebo-treated patients are shown in Table I. In brief, the placebo-treated patients showed no significant change in any of the out-

TABLE I.
Pretreatment versus Posttreatment Outcome Measures.*

	Roxithromycin Group (n = 29)		Placebo Group (n = 35)	
Outcome	Mean (SEM)	*P* value	Mean (SEM)	*P* value
PNIF (L/min)				
Pre-	102.7 (6.5)		104.3 (6.1)	
Post-	99.9 (7.8)	NS	104 (7.4)	NS
STT (min)				
Pre-	11.5 (1.2)		10.9 (0.8)	
Post-	8.2 (0.8)	<0.01	11.3 (1.0)	NS
Nasal endoscopy				
Pre-	3.2 (0.2)		3.0 (0.2)	
Post-	2.6 (0.2)	<0.01	2.9 (0.2)	NS
Olfactory function				
Pre-	22.5 (1.8)		22.7 (1.5)	
Post-	23.6 (1.7)	NS	22.3 (1.4)	NS
SNOT-20				
Pre-	2.75 (0.13)		2.83 (0.12)	
At 6 weeks	2.61 (0.14)	NS	2.87 (0.15)	NS
At 12 weeks	2.34 (0.19)	0.01	2.88 (0.12)	NS
At 24 weeks	2.49 (0.18)	NS	2.84 (0.15)	NS
Interleukin-8 (pg/ml)				
Pre-	226.6 (48.2)	NS	126.2 (15.6)	
Post-	156 (38.7)		194.2 (42.4)	NS
a2-macro (μg/ml)				
Pre-	1.87 (0.39)		1.63 (0.4)	
Post-	1.86 (0.72)	NS	1.88 (0.56)	NS
Fucose (μmol/l)				
Pre-	18.6 (3.5)		12.5 (1.6)	
Post-	21.5 (7.2)	NS	13.7 (2.3)	NS

*All patients in placebo and roxithromycin groups.
SEM, standard error of mean; PNIF, peak nasal inspiratory flow; STT, saccharine transit time; SNOT-20, Sinonasal Outcome Test-20; NS, not significant.

TABLE II.
Pretreatment versus Posttreatment Outcome Measures.*

	Low IgE group (n = 14)		High IgE group (n = 15)	
Outcome	Mean (SEM)	*P* value	Mean (SEM)	*P* value
PNIF				
Pre-	101.4 (12.0)		98.5 (10.4)	
Post-	102.4 (10.1)	NS	105.5 (11.1)	NS
STT				
Pre-	11.2 (1.3)		11.9 (0.8)	
Post-	7.5 (0.8)	<0.01	8.9 (1.3)	0.04
Nasal endoscopy				
Pre-	3.1 (0.3)		3.3 (0.3)	
Post-	2.1 (0.3)	<0.01	3.1 (0.3)	NS
Olfactory function				
Pre-	26.3 (2.4)		19.0 (2.3)	
Post-	28.3 (1.7)	NS	19.2 (2.4)	NS
SNOT-20				
Pre-	2.73 (0.24)		2.76 (0.16)	
At 6 weeks	2.49 (0.17)	NS	2.71 (0.15)	NS
At 12 weeks	2.03 (0.31)	<0.01	2.63 (0.19)	NS
At 24 weeks	2.24 (0.25)	0.06	2.85 (0.21)	NS
Interleukin-8 (pg/ml)				
Pre-	244.1 (82.7)		218.6 (55.1)	
Post-	98.2 (20.9)	0.02	201.2 (70.4)	NS
a2-macro (μg/ml)				
Pre	1.67 (0.52)	NS	2.02 (0.33)	
Post-	0.89 (0.25)		2.55 (0.42)	NS
Fucose (μmol/l)				
Pre-	17.5 (4.3)		19.5 (2.9)	
Post-	23.0 (10.7)	NS	20.1 (4.3)	NS

*Roxithromycin-treated patients with low IgE vs high IgE.
SEM, standard error of mean; PNIF, peak nasal inspiratory flow; STT, saccharine transit time; SNOT-20, Sinonasal outcome Test-20.

come measures. The roxithromycin-treated patients showed significant improvements in saccharine transit time ($P < .01$), nasal endoscopic scoring ($P < .01$), and SNOT-20 scoring ($P = .01$) at the completion of treatment. No significant improvements were noted in SNOT-20 scoring after 6 weeks of treatment or 3 months after the completion of treatment. In addition, no significant improvements were seen in peak nasal inspiratory flow, olfactory function scoring, and nasal lavages for IL-8, fucose, and α2-macroglobulin.

Roxithroymcin-Treated Patients With Low IgE versus High IgE

For the purpose of further analysis, subjects in the roxithromycin group were further divided into those with low (<200 μg/L) (n = 14) and high (>200 μg/L) (n = 15) levels of serum IgE. Pre- and posttreatment outcome measures were compared between these two groups and are discussed subsequently and demonstrated in Table II.

Patient Response Scale

The linear rating scale was compared for those roxithromycin-treated patients with low IgE versus those with high IgE. Patients in the low IgE group (2.5 $\pm$ 0.17; range, 2–4) differed significantly from the high IgE group (3.8 $\pm$ 0.14; range, 3–5) ($P < .01$).

Patients With Low Levels of IgE

Patients with low levels of IgE showed statistically significant reductions in saccharine transit time ($P < .01$) and nasal endoscopic scoring ($P < .01$). SNOT-20 scoring showed no significant improvement after 6 weeks of treatment; however, after 12 weeks, there were statistically significant improvements ($P < .01$). Twelve weeks posttreatment, the SNOT-20 scores were improved compared with the baseline levels but this improvement failed to reach significance ($P = .06$). No significant improvements were shown for peak nasal inspiratory flow and olfactory function scoring. Nasal lavages showed a significant reduction in Il-8 levels in the posttreatment lavages ($P = .02$). No significant reductions were seen in the fucose and α2-macroglobulin lavages.

Patients with High Levels of IgE

Roxithromycin treatment in this group of patients produced a significant reduction in saccharine transit time ($P = .04$). No significant improvement was noted in any of the remaining outcome measures or in the nasal lavages.

DISCUSSION

At the time of writing, this study represents the first double-blind, randomized, placebo-controlled trial of long-term, low-dose macrolide in the treatment of chronic rhinosinusitis. We have shown that roxithromycin, when compared with placebo, is capable of producing significant improvements in a range of subjective and objective outcome measures. This effect is particularly evident in patients with low levels of IgE.

Patients receiving roxithromycin reported significant improvements in the linear rating scale and in their SNOT-20 scores after the 12-week course. Interestingly, these improvements were not noted after only 6 weeks of treatment. These findings are consistent with previous studies that have suggested that a prolonged course of macrolide is required before a clinical effect is seen. Hashiba[5] reported that response rates of chronic rhinosinusitis patients were 5% at 2 weeks at 71% at 12 weeks. Similarly, Cervin[6] showed that patients who had a response after 3 months of treatment showed continued improvement in symptom scores, nasal nitric oxide, and ciliary beat frequency after 12 months of macrolide. Our study therefore supports the use of relatively long-term courses of macrolide antibiotics in the treatment of chronic rhinosinusitis.

To assess any long-term benefit of the 12-week macrolide treatment, patients were assessed after a further 12 weeks after the cessation of treatment. The benefits of treatment were not sustained; SNOT-20 scores 12 weeks after treatment were similar to pretreatment scores. Patients with low levels of IgE did show improved SNOT-20 scores but these failed to reach statistical significance ($P = .06$). This finding suggests that treatments longer than 12 weeks are necessary, or perhaps multiple courses of macrolide may be required to maintain the beneficial effect. Such treatments may create problems with side effects and compliance, especially if the benefit is not marked. This issue has not been addressed in previous studies.

The observed benefits of macrolide treatment were only evident after 12 weeks of treatment. Such long-term treatment could lead to the emergence of resistant organisms. In our study, middle meatal swabs performed before and after treatment failed to show any macrolide-resistant organisms; however, the small number of patients examined precludes any firm conclusion regarding the likelihood of resistant organisms developing.

Previous authors have suggested that macrolide treatment may be most beneficial in those patients with low levels of IgE. This suggestion is partly based on the fact that macrolides exert an inhibitory effect on promoters of neutrophilic inflammation such as interleukin-8.[1,14] Suzuki et al.,[15] in a study of 16 patients with chronic rhinosinusitis, reported that symptomatic improvement correlated with low levels of IgE and with low eosinophil counts in peripheral blood, nasal smears, and nasal mucosa. In the present study, we performed a subgroup analysis on patients with low levels of IgE compared with those with high levels. Patients with low levels of IgE showed significant improvements in symptom scores, saccharine transit time, nasal endoscopic scoring, and nasal lavage levels of interleukin-8. Patients with high IgE levels showed a significant improvement only in saccharine transit time. In addition, the low IgE patients had a significantly improved final linear rating scale compared with the high IgE group. We believe that these findings provide further evidence that there is a subgroup of patients with chronic rhinosinusitis who are more likely to benefit from macrolides and that levels of IgE may be a useful tool in selecting patients for treatment.

The findings of this study have raised a number of additional questions regarding the role of macrolides in clinical practice. As discussed here, the longevity of the treatment effect and the optimal duration of treatment are unknown. In addition, the actual benefit that patients experience with macrolide treatment needs to be weighed against the risks of side effects and the danger of development of resistant bacteria. It is worth noting in this study that although the linear rating scale did show significant improvements in patients receiving macrolide antibiotics, none of these patients reported that they were "completely improved." Further studies with larger numbers of patients, further subgroup analysis, and longer follow up may help to answer these questions.

CONCLUSION

We have reported the first double-blind, randomized, placebo-controlled trial of macrolide antibiotics in the treatment of chronic rhinosinusitis and have demonstrated improvements in both subjective and objective outcome measures. These improvements were particularly evident in patients with low levels of IgE. The findings of this study are consistent with the known antiinflammatory effect of macrolides in chronic airway inflammation. Additional studies are required to assess the exact role of macrolides in clinical practice.

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BIBLIOGRAPHY

1. Wallwork B, Coman W, Feron F, et al. Clarithromycin and prednisolone inhibitcytokine production in chronic rhinosinusitis. *Laryngoscope* 2002;112:1827–1830.
2. Wozniak DJ, Keyser R. Effects of subinhibitory concentrations of macrolide antibiotics on *Pseudomonas aeruginosa*. *Chest* 2004;125:62S–69S; quiz 69S.
3. Inamura K, Ohta N, Fukase S, et al. The effect of erythromycin on human peripheral neutrophil apoptosis. *Rhinology* 2000;38:124–129.
4. Miyanohara T, Ushikai M, Matsune S, et al. Effects of clarithromycin on cultured human nasal epithelial cells and fibroblasts. *Laryngoscope* 2000;110:126–131.
5. Hashiba M, Baba S. Efficacy of long-term administration of

clarithromycin in the treatment of intractable chronic sinusitis. *Acta Otolaryngol* 1996:73–78.
6. Cervin A, Kalm O, Sandkull P, et al. One-year low-dose erythromycin treatment of persistent chronic sinusitis after sinus surgery: clinical outcome and effects on mucociliary parameters and nasal nitric oxide. *Otolaryngol Head Neck Surg* 2002;126:481–489.
7. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope* 2004;114: 923–930.
8. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997;117:S1–7.
9. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology* 1993;31:183–184.
10. Leopold D, Ferguson BJ, Piccirillo JF. Outcomes assessment. *Otolaryngol Head Neck Surg* 1997;117:S58–68.
11. Mackay-Sim A, Grant L, Owen C, et al. Australian norms for a quantitative olfactory function test. *J Clin Neurosci* 2004;11:874–879.
12. Kobal G, Klimek L, Wolfensberger M, et al. Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. *Eur Arch Otorhinolaryngol* 2000;257:205--211.
13. Greiff L, Andersson M, Coman WB, et al. Challenge-induced plasma exudation and mucinous secretion in human airways. *Clin Physiol Funct Imaging* 2005;25:241–245.
14. Suzuki H, Ikeda K. Mode of action of long-term low-dose macrolide therapy for chronic sinusitis in the light of neutrophil recruitment. *Curr Drug Targets Inflamm Allergy* 2002;1:117–126.
15. Suzuki H, Ikeda K, Honma R, et al. Prognostic factors of chronic rhinosinusitis under long-term low-dose macrolide therapy. *ORL J Otorhinolaryngol Relat Spec* 2000;62: 121–127.