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Macrolide therapy for chronic rhinosinusitis: A meta-analysis

Melissa A. Pynnonen, MD¹, Giri Venkatraman, M.D., M.B.A.², and Greg Davis, M.D., M.P.H.³

¹Department of Otolaryngology, University of Michigan Health System, Ann Arbor, MI

²Section of Otolaryngology, Dartmouth-Hitchcock Medical Center, Lebanon, NH

³Department of Otolaryngology, University of Washington, Seattle, WA

Abstract

Objective—The objective of this study was to systematically review patient reported outcomes of long term macrolide therapy, compared with any other treatment, for adults with chronic rhinosinusitis.

Data Sources—Embase and PubMed databases were searched in October, 2011.

Review Methods—A total of 1216 citations were screened initially by a single author, 23 full text manuscripts were evaluated by 2 authors using structured data abstraction forms to assess for inclusion criteria and study quality, and 3 studies were included in the final review.

Results—This review finds that there are 3 prospective clinical studies which evaluate the effect of macrolide therapy for chronic rhinosinusitis. Based on the limited data, there is limited scientific evidence to support the use of long term macrolide therapy for chronic rhinosinusitis.

Conclusion—Further clinical research is needed to determine whether there may be a subgroup effect based on the underlying inflammatory disease process.

Keywords

Rhinitis/*medical therapy; Sinusitis/*medical therapy; macrolide; chronic rhinosinusitis; chronic sinusitis; human; adult; meta-analysis

Introduction

Sinusitis is one of the most common chronic conditions in the United States, purportedly affecting up to 13% of the adult population.¹ Chronic rhinosinusitis (CRS) may be treated with medical or surgical therapy and many patients require a combination of both. Among medical therapy, treatment is selected based on the presumed pathophysiology. For example, chronic bacterial infection is treated with culture-guided antibiotic therapy whereas allergy is treated with allergen avoidance, immunotherapy, antihistamines, or corticosteroids.²

Most patients with CRS have symptoms of nasal obstruction, facial congestion, hyposmia, and rhinorrhea. These symptoms are caused by a chronic inflammatory process that

Melissa A. Pynnonen, MD, Department of Otolaryngology, 1904 Taubman Center, University of Michigan Hospitals, Ann Arbor, MI 48109, pynnonen@umich.edu, (734) 232-0120 (phone), (734) 936-9625 (fax) .

improves with nasal or oral corticosteroids. In addition to corticosteroids, another medication class with anti-inflammatory properties is macrolide antibiotics.^{3–5} Multiple clinical trials have studied macrolide therapy for chronic sinusitis treatment and have reported mixed results. As a result, despite the prevalence of chronic sinusitis, we still don't have a clear understanding of the best medical treatment for the majority of affected patients.

In this context of uncertain benefit of medical treatment and the reportedly high prevalence of the disease, it was our objective to answer this question: In adult patients with chronic rhinosinusitis, what is the disease specific quality of life impact of long term macrolide therapy, compared to any other treatment?

Methods

Objective and a prior inclusion criteria

We followed the preferred reporting items for systematic reviews and meta-analyses.⁶ Through consensus opinion, we developed a priori inclusion and exclusion criteria. We included only studies in which CRS was diagnosed in a manner consistent with either the AAO-HNS Task Force criteria⁷ or the European Position Paper on Rhinosinusitis and Nasal Polyps.⁸ This included the presence of 12 or more weeks of two or more of the following symptoms: mucopurulent rhinorrhea or post nasal drainage, nasal obstruction, facial pressure, or decreased smell; and evidence of inflammation in the middle meatus as demonstrated on physical examination, nasal endoscopy, or on a radiographic study. This definition of CRS is consistent with a recently published systematic review.⁹ We restricted the intervention to studies of oral macrolide therapy. In the interest of assessing the potential role of “maximal medical therapy” we did not exclude studies which included therapies in addition to macrolide antibiotic. We excluded studies that did not include a non-macrolide comparator group. We excluded studies that did not report disease specific or symptom based outcomes. We excluded studies limited to post-operative therapy or pediatric patients. We excluded retrospective studies. We elected a priori to exclude studies published in non-English languages.

Information sources and searches

A computerized EMBASE search was performed on October 12, 2011. Subject headings for sinusitis and rhinitis with subheading drug therapy, or subject headings or keywords for chronic sinusitis, chronic rhinitis or rhinosinusitis were combined with subject headings and keywords representing macrolides. MEDLINE records were excluded to reduce duplication. No additional date or publication limits were applied.

A computerized PubMed search of MEDLINE 1966–October 14, 2011 was performed. Articles mapping to the subject heading “macrolides” or keywords “macrolides” or “macrolide” in the title or abstract were cross referenced with articles mapping to subject heading “sinusitis” or “rhinitis” or keywords “chronic rhinosinusitis” or “chronic sinusitis” or “chronic rhinitis” in the article title or abstract. No additional date or publication limits were applied.

Data collection process

Prior to data collection, we established our data collection form and pilot tested it across all 3 authors. We clarified ambiguities within the form and discrepancies in data collection. Following consensus, we implemented the form for study purposes. The data collection form content was as follows.

Verification of study eligibility—inclusion and exclusion criteria, definition of CRS (a method consistent with the Rhinosinusitis Task Force⁷ or European Position Paper on Rhinosinusitis and Nasal Polyps⁸), and Institutional Review Board or other ethics review board approval

Methods—allocation concealment (adequate, unclear, inadequate, not used), method of concealment, study design (parallel design RCT, cross-over RCT, other), patient blinding (yes, no, unclear), provider blinding (yes, no, unclear), analyst blinding (yes, no, unclear), co-interventions or protocol deviations in addition to macrolide or comparator therapy, other potential confounders.

Participants—number of subjects enrolled per group, age, gender, drop outs, reasons for drop out, comorbidities.

Interventions—macrolide type, dose, and duration. Comparator therapy or placebo description.

Outcomes—outcome assessed (e.g. individual symptoms, overall symptom score, quality of life instrument), method of assessment, timing of assessment, length of follow up.

Risk of bias—residual confounding, lack of blinding, reporting bias, attrition bias, absence of an a priori treatment protocol, absence of an a priori analysis protocol.

Statistical Analysis

We compared SNOT-20 change scores between groups using a 2 group t test and patient level data using STATA 12.0 (StataCorp College Station, TX). We performed meta-analysis with formulas provided by Review Manager, Version 5.1 (Copenhagen, Denmark).¹⁰ We used a fixed effects inverse variance model to compare standardized mean differences (SMD) in two versions of the Sinonasal Outcome Test (SNOT) (SNOT-20 and SNOT-22). We used this same model to compare ordinal patient response scales across studies.

We assessed heterogeneity. Heterogeneity indicates the treatment effect is different across studies and is detected when the variation between studies is greater than the amount of variation expected by chance. We calculated a Cochrane's Q test (which follows a χ^2 distribution) and the I^2 statistic (which measures the proportion of inconsistency in individual studies that cannot be explained by chance). For Cochrane's Q test, 0% indicates minimum heterogeneity and 100% maximum heterogeneity. For the I^2 statistic, a small p value indicates greater likelihood of heterogeneity.¹¹

Results

Search results and study selection

The EMBASE search yielded 650 references and the PubMed search of MEDLINE yielded 570 references. The searches were combined.

Based upon review of titles and available abstracts, a single author (MP) excluded 1192 articles because they were either duplicates or did not meet a priori inclusion criteria. Twenty-four articles remained for which we obtained the complete articles. Each study was reviewed in its entirety by two authors who screened the study for inclusion based on a priori criteria described above. We compared notes between the authors during the data abstraction process. Disagreements were settled through discussion to reach consensus. We excluded a further 18 studies. Articles were hand-searched for additional references for inclusion, but none met a priori criteria. Six studies were then reviewed and data collection forms were completed by all three authors. Two additional studies were excluded because they were deemed out of scope^{12,13} and one additional study was excluded because it used a definition of CRS that was not consistent with either the Rhinosinusitis Task Force or European Position Paper on Rhinosinusitis and Nasal Polyps.¹⁴ Three studies were included in the final systematic review. Figure 1

Study characteristics

Characteristics of the included studies are listed in Table 1. The 3 studies were similar in size (59–64 subjects) and in the patient populations included. Two studies excluded patients with nasal polyps^{15,16} and one study excluded patients with massive polyposis.¹⁶ The frequency and duration of macrolide treatment varied across the three studies. Amini et al.¹⁵ treated patients with clarithromycin daily for 3 weeks. Videler et al.¹⁷ treated patients with azithromycin for 3 days during week 1, then weekly for 11 weeks. Wallwork et al.¹⁶ treated patients with roxithromycin daily for 12 weeks. Comparator treatment also varied. Amini et al.¹⁵ provided the comparator group with amoxicillin/clavulanic acid 3 times daily for 3 weeks; Videler et al.¹⁷ and Wallwork et al.¹⁶ both provided the comparator group with placebo.

Outcomes assessed varied across the studies (Table 2). Amini et al.¹⁵ assessed 7 individual nasal symptoms at the conclusion of the 8-week study and found no statistically significant difference for any of the symptoms.

Videler et al.¹⁷ assessed outcomes at 3 time points during active treatment phase (weeks 6, 12, and 14) and once following treatment conclusion (week 24). They used 4 patient oriented outcome measures: an unvalidated patient response scale (desperately worse, worse, no change, improvement, and cured), visual analogue scales for 17 symptoms, short-form-36 (SF-36) for general health status, and the SNOT-22 (scale 0–110) for disease specific quality of life. They report a statistically significant difference in the patient response scale at week 24 favoring the macrolide group. They report only one difference in assessment of 17 symptoms, favoring the placebo group at week 12 for facial pain. The only difference in SF-36 scores was in bodily pain at 6 weeks. They report no difference in SNOT-22 scores at any time point.

Wallwork et al.¹⁶ assessed outcomes twice during the 12 week active treatment phase (weeks 6 and 12) and once following treatment conclusion (week 24). They used 2 patient-oriented outcome measures: the SNOT-20 and an unvalidated patient response scale (completely improved, much improved, slightly improved, not improved, slightly worse, much worse). They reported outcomes by treatment group, macrolide versus placebo. They also reported outcomes based on subgroup analysis by low (<200 µg/L) and high (>200 µg/L) serum IgE level.

The authors report a significant difference in the patient response scale at 12 weeks ($p<0.01$) favoring the macrolide group. They also report the subgroup with low IgE levels improved significantly more than patients with high IgE levels.

The authors did not report between group differences in SNOT-20 change scores (i.e. how the macrolide group compared with the placebo group). However, we were able to obtain patient level data and calculate between group differences in SNOT-20 change scores (Unpublished data from Wallwork, correspondence in 2012). We found a statistically significant difference at week 24 favoring the macrolide group. We also compared SNOT-20 change scores by IgE subgroups. Among the low IgE subgroup, we found statistically significant differences at all 3 time points favoring the macrolide group. However, given that the minimum clinically significant change in the SNOT-20 is believed to be 0.8, the SNOT-20 changes within the macrolide group (week 24 -0.22) and the low IgE subgroup (6 week -0.31, 12 week -0.70, 24 week -0.56) are likely not clinically significant.¹⁸

Two studies, Videler¹⁷ and Wallwork¹⁶, reported SNOT scores and patient response scale measures permitting meta-analysis (unpublished data from Videler, correspondence in 2012). One hundred and nineteen patients were randomized into these two studies. We compared SNOT scores at 6, 12, and 24 weeks, calculating standardized mean differences. We identified a statistically significant difference favoring macrolide therapy at 24 weeks with a standardized mean difference of -0.43, $p=0.03$ (Figure 2). The standardized mean difference, when multiplied by the standard deviation, provides an estimate of expected change for an average patient. Thus a standardized mean difference of -0.43 on the SNOT-20 (0–5 scale, 0.8 SD) equates to a 0.34 point decrease in SNOT score.¹⁸ Once again, this is likely clinically insignificant. Heterogeneity was moderate and not significant ($I^2=45\%$, χ^2 test, $p=0.18$). Comparisons of the SNOT scores at 6 and 12 weeks found no significant differences between macrolide therapy and placebo (Figures 3 and 4). Comparison of the patient response scale found a statistically significant difference at 12 weeks ($p<0.001$), but with extreme and statistically significant heterogeneity ($I^2=98\%$, χ^2 test, $p<0.001$) that is difficult to interpret (Figure 5).

Discussion

Medical treatment for CRS is often directed at the underlying chronic inflammatory process. Macrolide antibiotics are often used in this capacity. The anti-inflammatory properties^{3–5} of macrolides is believed to occur through down regulation of proinflammatory cytokines including Interleukin-8 (IL-8), a potent neutrophil chemoattractant.¹⁹ As a result, inhibition of IL-8 may suppress inflammatory pathways which contribute to CRS. Indeed, many

publications, particularly in the Japanese literature, attest to the benefit of macrolide therapy for the treatment of nasal manifestations of “sinobronchial syndrome”.^{3,4} Nonetheless, in this meta-analysis of English language studies, we do not find convincing evidence of clinically significant symptom improvement with macrolide therapy compared to placebo.

In this review we found statistically significant, but likely clinically insignificant, improvement in a validated outcome measure—the SNOT scale—at a single time point only (24 weeks). Analysis using a second outcome measure, an unvalidated patient response scale, does not allow us to make any conclusions because of the substantial heterogeneity between studies. The heterogeneity may be related to a couple of factors that should be accounted for in subsequent clinical research on this topic. First, a subgroup effect may be present with greater response to macrolide therapy in patients with low IgE levels. This was suggested by the subgroup results in Wallwork¹⁶. Such a subgroup effect is consistent with the macrolide mechanism of action. Macrolides suppress promoters of neutrophilic inflammation such as interleukin-8. As a result, patients in the high IgE subgroup—with eosinophilic dominated CRS—may be less likely to benefit from macrolide therapy compared to those in the low IgE subgroup. Unfortunately, this analysis was unable to tease out a significant subgroup effect because we lacked a sufficient number of studies with subgroup data. Future studies of macrolide therapy should collect and report inflammatory markers to permit *a priori* subgroup analysis.

A second factor that may have contributed to extreme heterogeneity on the patient response scale is potential bias within these unvalidated instruments. The scale used by Wallwork was biased. It included 3 points to describe improvement, a neutral point, and 2 points to describe worsening. In contrast, the scale used by Videler was unbiased. It included 2 points to describe improvement, a neutral point, and 2 points to describe worsening. These two scales effectively highlight the value of unbiased and validated outcome measures.

The limitations of this meta-analysis reflect limitations of the individual studies, the limited number of individual studies available for inclusion, and the absence of funding to pay for translation of Japanese publications.

In summary, Amini et al.¹⁵ found no difference between groups; Videler et al.¹⁷ and Wallwork et al.¹⁶ each found limited evidence of benefit with macrolide therapy. Meta-analysis of SNOT scores demonstrated statistically significant but clinically insignificant benefit to macrolide therapy at a single time point. Altogether, the three studies included in this review do not demonstrate evidence for a clinically significant impact of long-term macrolide therapy for CRS. Future studies should include *a priori* subgroup analysis based on inflammatory marker profiles, to determine whether there may be a clinically important subgroup effect favoring patients with low serum IgE.

Description of excluded studies

Three studies passed initial selection criteria but were subsequently excluded from the final review through group discussion. We will discuss those studies briefly. The study by Ragab *et al* was an RCT containing two arms of treatment.¹⁴ All subjects were exposed to a run-in period during which time they were treated medically. Subjects who failed to improve with

medical therapy were subsequently enrolled in the RCT. Subjects were randomized to either medical treatment with macrolide therapy or to surgical treatment. This study was excluded because the authors used a definition of CRS that, upon careful reflection, did not meet our *a priori* criteria. This study defined CRS as the presence of 8 weeks of symptoms—not the 12 weeks needed to meet the AAO-HNS Task Force criteria⁷ or the European Position Paper on Rhinosinusitis and Nasal Polyps for diagnosis of CRS.⁸ Two additional studies were deemed to be out of scope because there was no non-macrolide comparator group.^{12,13} The retrospective study by Haruna *et al*¹³ compared roxithromycin with clarithromycin and sought to differentiate the clinical effect of macrolide therapy based on the presence of allergic rhinitis, nasal polyposis, or tissue eosinophilia. The study by Majima *et al*¹² was an RCT comparing clarithromycin therapy with combination therapy of clarithromycin and S-carboxymethylcysteine, a mucolytic. Both of these studies were deemed to be out of the scope of this review because there was no non-macrolide comparator arm and no opportunity to evaluate the effects of macrolide treatment.

Conclusion

In conclusion, the current evidence demonstrates there is no clinically significant improvement in patient-oriented quality of life measures with long term macrolide therapy for CRS. However, there may be an effect among the subgroup of patients with low serum IgE. Further studies in this area should be designed and adequately powered for *a priori* subgroup analysis based on IgE and other inflammatory marker profiles.

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Figure 1.
Flow Chart of Study Selection

Figure 2.
 Sinonasal Outcome Test Change Scores at 6 weeks

Figure 3.
 Sinonasal Outcome Test Change Scores at 12 weeks

Figure 4.
 Sinonasal Outcome Test Change Scores at 24 weeks

Figure 5.
 Patient Response Scale at 12 weeks

Table 1

Characteristics of included studies

Author, year	Study Design	Sample size	Treatment	Comparator	Treatment duration
Amini, 2009 ¹⁵	RCT	59	Clarithromycin XL 500mg daily, pseudoephedrine, bromhexine, beclomethasone spray	Amoxicillin /clavulanic acid 625mg TID, pseudoephedrine, bromhexine, beclomethasone spray	3 weeks
Videler, 2011 ¹⁷	RCT	60	Azithromycin 500mg daily for 3 days; 500mg weekly for 11 weeks	Placebo	12 weeks
Wallwork, 2006 ¹⁶	RCT	64	Roxithromycin 150mg daily for 3 months	Placebo	12 weeks

Abbreviations: RCT, Randomized controlled trial; TID, three times daily

Table 2

Outcomes of included studies

Author, year	Outcome measure	Between group comparison																												
Amini, 2009 ¹⁵	Nasal symptoms “Improved, unchanged, or worsened” Symptoms assessed: post nasal drip, headache, cough, rhinorrhea, epistaxis, facial pain or pressure, nasal congestion 8 week follow up	Nasal symptoms No difference for any symptom at 8 weeks (P = 0.05)																												
Videler, 2011 ¹⁷	Patient response scale “Desperately worse, worse, same, improvement, cured” Nasal symptoms , rated with VAS. Headache, obstruction, rhinorrhea, postnasal drip, fullness, hyposmia, facial pain, general health, tiredness, cough, nasal crusts, epistaxis, tears, tooth pain, nausea, vomiting, diarrhea Short Form-36 assesses eight domains: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health SNOT-22 Negative change score indicates improvement 24 week follow up	Patient response scale No benefit to macrolide treatment at 6, 12, or 14 weeks (P=0.323, P=0.788, P=0.671) 24 week comparison favored macrolide group (P=0.017) Nasal symptoms 12 week comparison for facial pain favored placebo (P=0.047) Short Form-36 6 week comparison for bodily pain favored macrolide treatment P=0.004) SNOT-22 mean (SD) change scores <table><tr><th></th><th><u>Treatment</u></th><th><u>Placebo</u></th><th><u>P value</u></th></tr><tr><td>6 week</td><td>-5.7 (15.6)</td><td>-2.7 (12.8)</td><td>0.378</td></tr><tr><td>12 week</td><td>-3.6 (21.7)</td><td>-8.1 (16.8)</td><td>0.192</td></tr><tr><td>14 week</td><td>-3.7 (16.7)</td><td>-8.9 (15.6)</td><td>0.298</td></tr><tr><td>24 week</td><td>-8.5 (20.3)</td><td>-5.2 (18.9)</td><td>0.528</td></tr></table>		<u>Treatment</u>	<u>Placebo</u>	<u>P value</u>	6 week	-5.7 (15.6)	-2.7 (12.8)	0.378	12 week	-3.6 (21.7)	-8.1 (16.8)	0.192	14 week	-3.7 (16.7)	-8.9 (15.6)	0.298	24 week	-8.5 (20.3)	-5.2 (18.9)	0.528								
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Wallwork, 2006 ¹⁶	Patient response scale “completely improved, much improved, slightly improved, not improved, slightly worse, much worse” SNOT-20 Negative change score indicates improvement 24 week follow up	Patient response scale, mean (SD) <table><tr><th></th><th><u>Treatment</u></th><th><u>Placebo</u></th><th><u>P value</u></th></tr><tr><td>12 week</td><td>3.11 (0.17)</td><td>3.84 (0.12)</td><td><0.01</td></tr></table> SNOT-20 mean change scores <table><tr><th></th><th><u>Treatment</u></th><th><u>Placebo</u></th><th><u>Difference</u></th><th><u>95% CI</u></th></tr><tr><td>6 week</td><td>-0.11</td><td>0.052</td><td>0.17</td><td>-0.12, 0.45</td></tr><tr><td>12 week</td><td>-0.41</td><td>-0.18</td><td>0.23</td><td>-0.17, 0.62</td></tr><tr><td>24 week</td><td>-0.22</td><td>0.39</td><td>0.61</td><td>0.15, 1.07</td></tr></table>		<u>Treatment</u>	<u>Placebo</u>	<u>P value</u>	12 week	3.11 (0.17)	3.84 (0.12)	<0.01		<u>Treatment</u>	<u>Placebo</u>	<u>Difference</u>	<u>95% CI</u>	6 week	-0.11	0.052	0.17	-0.12, 0.45	12 week	-0.41	-0.18	0.23	-0.17, 0.62	24 week	-0.22	0.39	0.61	0.15, 1.07
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Table 3Mean SNOT-20 change scores by IgE level¹⁶

Low IgE subgroup				
	<u>Low IgE</u>	<u>Placebo</u>	<u>Difference</u>	<u>95% CI</u>
6 week	-0.31	0.052	0.362	0.055, 0.67
12 week	-0.70	-0.18	0.52	0.077, 0.97
24 week	-0.56	0.39	0.96	0.45, 1.47
High IgE subgroup				
	<u>High IgE</u>	<u>Placebo</u>	<u>Difference</u>	<u>95% CI</u>
6 week	0.10	0.052	- 0.48	-0.39, 0.29
12 week	-0.085	-0.18	-0.095	-0.59, 0.40
24 week	0.18	0.39	0.21	-0.37, 0.78