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Macrolide Therapy for Chronic Rhinosinusitis: A Meta-analysis

Melissa A. Pynnonen, MD¹, Giri Venkatraman, MD², and Greg E. Davis, MD, MPH³

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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 3 prospective clinical studies have evaluated 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, sinusitis, macrolide, chronic rhinosinusitis, chronic sinusitis, human, adult, meta-analysis

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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 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 do not 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 with any other treatment?

Methods

Objective and A Priori 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 American Academy of Otolaryngology—Head and Neck Surgery (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 2 or more of the following symptoms: mucopurulent rhinorrhea or postnasal drainage; nasal obstruction, facial pressure, or decreased smell; and evidence of inflammation in the middle meatus as demonstrated on physical examination, nasal endoscopy, or a radiographic study. This definition of CRS is consistent with a recently published

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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 that included therapies in addition to macrolide antibiotic. We excluded studies that did not include a nonmacrolide comparator group, studies that did not report disease-specific or symptom-based outcomes, studies limited to postoperative therapy or pediatric patients, and 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 to 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 randomized controlled trial [RCT], crossover RCT, other), patient blinding (yes, no, unclear), provider blinding (yes, no, unclear), analyst blinding (yes, no, unclear), coin-terventions or protocol deviations in addition to macrolide or comparator therapy, and other potential confounders

Participants: number of subjects enrolled per group, age, sex, dropouts, reasons for dropout, and comorbidities

Interventions: macrolide type, dose, and duration; comparator therapy or placebo description

Outcomes: outcome assessed (eg, individual symptoms, overall symptom score, quality-of-life instrument),

method of assessment, timing of assessment, and length of follow-up

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

Statistical Analysis

We compared Sinonasal Outcome Test–20 (SNOT-20) change scores between groups using a 2-group *t* test and patient-level data using STATA 12.0 (StataCorp, College Station, Texas). 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 in 2 versions of the 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 646 references and the PubMed search of MEDLINE yielded 570 references. The searches were combined.

On the basis of a review of titles and available abstracts, a single author (M.A.P.) excluded 1192 articles because they were either duplicates or did not meet a priori inclusion criteria. Twenty-three articles remained for which we obtained the complete articles. Each study was reviewed in its entirety by 2 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 17 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 3 authors. Two additional studies were excluded because they were deemed out of scope,^{12,13} and 1 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

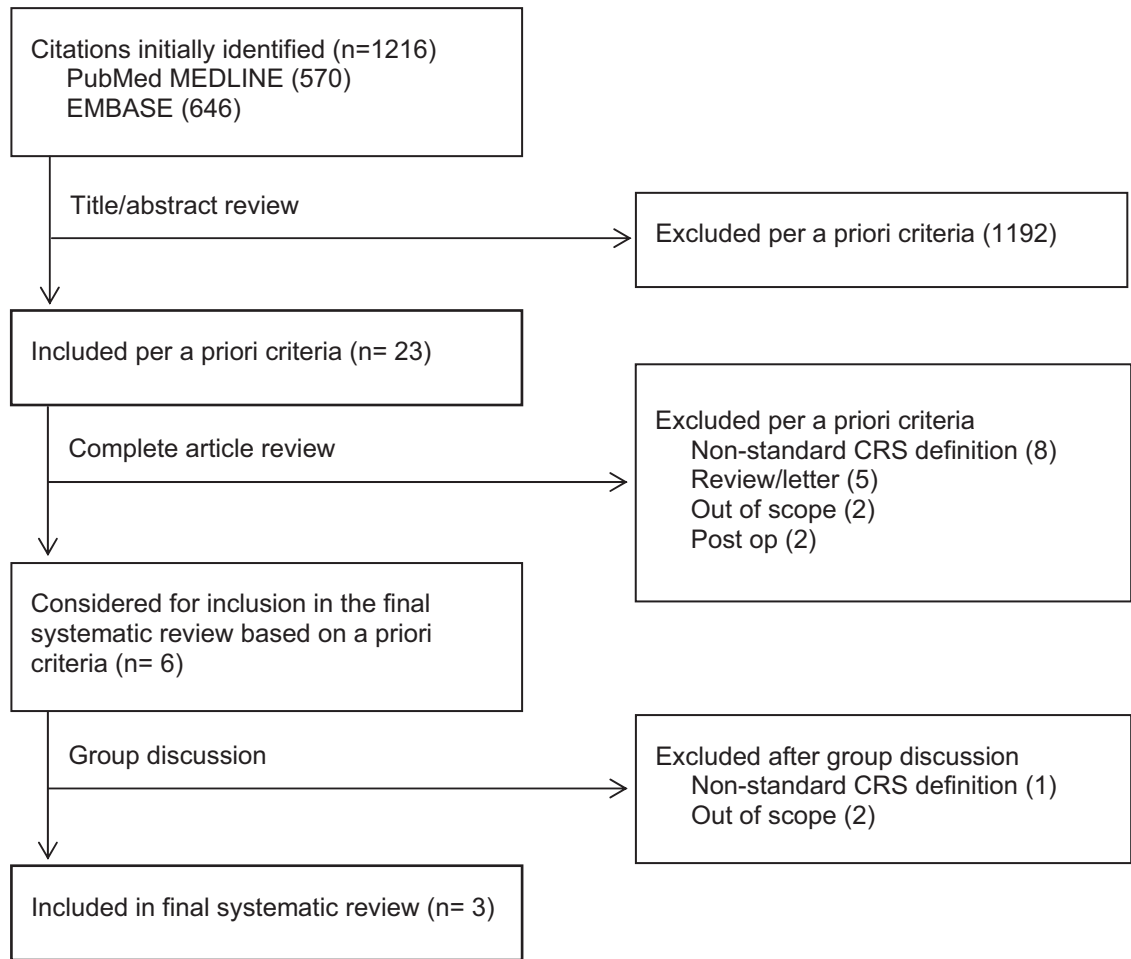


Figure 1. Flowchart of study selection. CRS, chronic rhinosinusitis.

Table 1. Characteristics of Included Studies

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

Abbreviations: RCT, randomized controlled trial; tid, 3 times daily.

the patient populations included. Two studies excluded patients with nasal polyps,^{15,16} and 1 study excluded patients with massive polyposis.¹⁶ The frequency and duration of macrolide treatment varied across the 3 studies. Amini et al¹⁵ treated patients with clarithromycin daily for 3 weeks. Videler et al¹⁷ treated patients with azithromycin for 3 days

during week 1, then weekly for 11 weeks. Wallwork et al¹⁶ treated patients with roxithromycin daily for 12 weeks. Comparator treatment also varied. Amini et al¹⁵ provided the comparator group with amoxicillin/clavulanic acid 3 times daily for 3 weeks; Videler et al¹⁷ and Wallwork et al¹⁶ both provided the comparator group with placebo.

Table 2. Outcomes of Included Studies

Author, Year	Outcome Measure	Between-Group Comparison																												
Amini et al, 2009 ¹⁵	Nasal symptoms “Improved, unchanged, or worsened.” Symptoms assessed: postnasal 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 ($P \geq .05$)																												
Videler et al, 2011 ¹⁷	Patient response scale “Desperately worse, worse, same, improvement, cured” Nasal symptoms Rated with visual analog scale. 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 8 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 ($P = .323$, $P = .788$, $P = 0.671$) 24-week comparison favored macrolide group ($P = .017$) Nasal symptoms 12-week comparison for facial pain favored placebo ($P = .047$) Short Form-36 6-week comparison for bodily pain favored macrolide treatment ($P = .004$) SNOT-22 mean (SD) change scores <table><tr><td></td><td>Treatment</td><td>Placebo</td><td>P Value</td></tr><tr><td>6 weeks</td><td>-5.7 (15.6)</td><td>-2.7 (12.8)</td><td>.378</td></tr><tr><td>12 weeks</td><td>-3.6 (21.7)</td><td>-8.1 (16.8)</td><td>.192</td></tr><tr><td>14 weeks</td><td>-3.7 (16.7)</td><td>-8.9 (15.6)</td><td>.298</td></tr><tr><td>24 weeks</td><td>-8.5 (20.3)</td><td>-5.2 (18.9)</td><td>.528</td></tr></table>		Treatment	Placebo	P Value	6 weeks	-5.7 (15.6)	-2.7 (12.8)	.378	12 weeks	-3.6 (21.7)	-8.1 (16.8)	.192	14 weeks	-3.7 (16.7)	-8.9 (15.6)	.298	24 weeks	-8.5 (20.3)	-5.2 (18.9)	.528								
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Wallwork et al, 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><td></td><td>Treatment</td><td>Placebo</td><td>P Value</td></tr><tr><td>12 weeks</td><td>3.11 (0.17)</td><td>3.84 (0.12)</td><td><.01</td></tr></table> SNOT-20 mean change scores <table><tr><td></td><td>Treatment</td><td>Placebo</td><td>Difference</td><td>95% CI</td></tr><tr><td>6 weeks</td><td>-0.11</td><td>0.052</td><td>0.17</td><td>-0.12 to 0.45</td></tr><tr><td>12 weeks</td><td>-0.41</td><td>-0.18</td><td>0.23</td><td>-0.17 to 0.62</td></tr><tr><td>24 weeks</td><td>-0.22</td><td>0.39</td><td>0.61</td><td>0.15 to 1.07</td></tr></table>		Treatment	Placebo	P Value	12 weeks	3.11 (0.17)	3.84 (0.12)	<.01		Treatment	Placebo	Difference	95% CI	6 weeks	-0.11	0.052	0.17	-0.12 to 0.45	12 weeks	-0.41	-0.18	0.23	-0.17 to 0.62	24 weeks	-0.22	0.39	0.61	0.15 to 1.07
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Abbreviations: CI, confidence interval; SNOT-20, Sinonasal Outcome Test–20; SNOT-22, Sinonasal Outcome Test–22.

Outcomes assessed varied across the studies (**Table 2**). Amini et al¹⁵ 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 al¹⁷ 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 analog 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 reported a statistically significant difference in the patient response scale at week 24 favoring the macrolide group. They reported only 1 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 reported no difference in SNOT-22 scores at any time point.

Wallwork et al¹⁶ assessed outcomes twice during the 12-week active treatment phase (weeks 6 and 12) and once

Table 3. Mean SNOT-20 Change Scores by IgE Level¹⁶

	Low IgE Subgroup			
	Low IgE	Placebo	Difference	95% CI
6 weeks	−0.31	0.052	0.362	0.055 to 0.67
12 weeks	−0.70	−0.18	0.52	0.077 to 0.97
24 weeks	−0.56	0.39	0.96	0.45 to 1.47
	High IgE Subgroup			
	High IgE	Placebo	Difference	95% CI
6 weeks	0.10	0.052	−0.48	−0.39 to 0.29
12 weeks	−0.085	−0.18	−0.095	−0.59 to 0.40
24 weeks	0.18	0.39	0.21	−0.37 to 0.78

Abbreviations: CI, confidence interval; SNOT-20, Sinonasal Outcome Test–20.

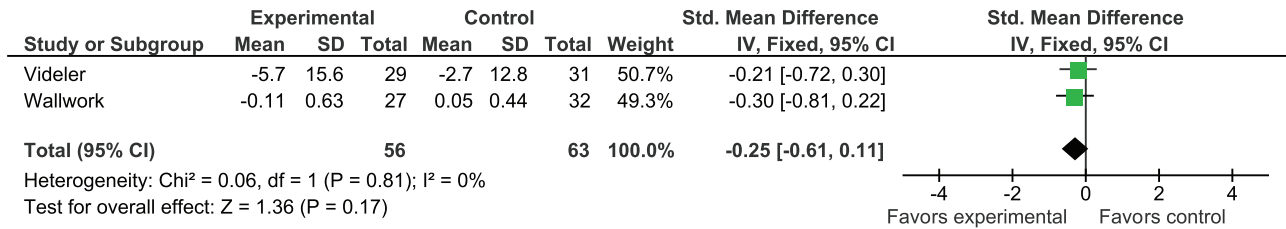


Figure 2. Sinonasal Outcome Test change scores at 6 weeks. CI, confidence interval.

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 vs placebo. They also reported outcomes based on subgroup analysis by low (<200 µg/L) and high (>200 µg/L) serum IgE level.

The authors reported a significant difference in the patient response scale at 12 weeks ($P < .01$) favoring the macrolide group. They also reported that 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 (ie, 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 (B. Wallwork, personal communication, 2012). We found a statistically significant difference at week 24 favoring the macrolide group. We also compared SNOT-20 change scores by IgE subgroups (Table 3). 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 weeks, −0.31; 12 weeks, −0.70; 24 weeks, −0.56) are likely not clinically significant.¹⁸

Two studies, by Videler et al¹⁷ and Wallwork et al,¹⁶ reported SNOT scores and patient response scale measures permitting meta-analysis (W. J. Videler, personal communication, 2012). One hundred nineteen patients were randomized into these 2 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, $P = .03$ (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 (SD) difference of −0.43 (0.8) on the SNOT-20 (0-5 scale) 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, $P = .18$). 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 ($P < .001$) but with extreme and statistically significant heterogeneity ($I^2 = 98\%$, χ^2 test, $P < .001$) 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 properties³⁻⁵ of macrolides are believed to occur through downregulation of

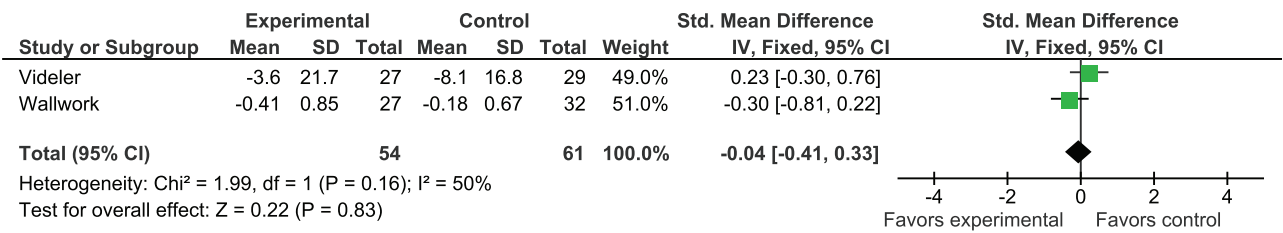


Figure 3. Sinonasal Outcome Test change scores at 12 weeks. CI, confidence interval.

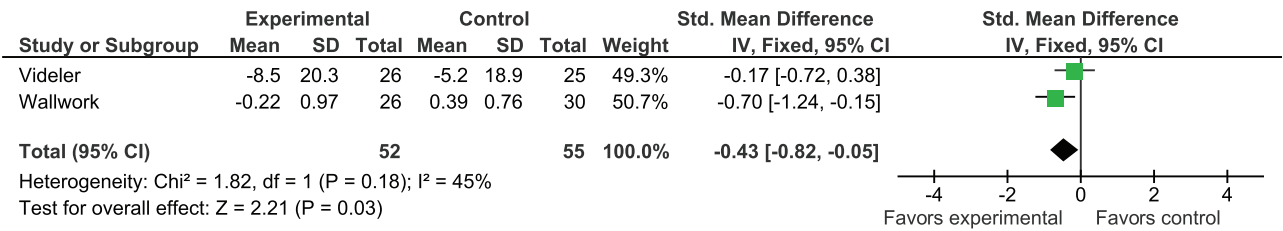


Figure 4. Sinonasal Outcome Test change scores at 24 weeks. CI, confidence interval.

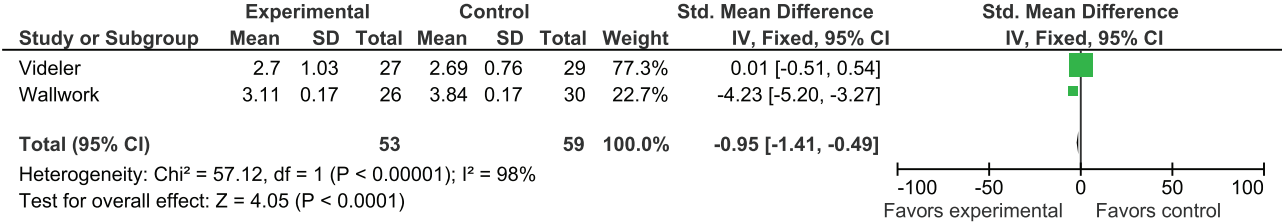


Figure 5. Patient response scale at 12 weeks. CI, confidence interval.

proinflammatory cytokines, including interleukin-8 (IL-8), a potent neutrophil chemoattractant.¹⁹ As a result, inhibition of IL-8 may suppress inflammatory pathways that 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 with 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 Wallwork et al.¹⁶ Such a subgroup effect is consistent with the macrolide mechanism of action.

Macrolides suppress promoters of neutrophilic inflammation such as IL-8. As a result, patients in the high IgE subgroup—with eosinophilic-dominated CRS—may be less likely to benefit from macrolide therapy compared with 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 et al¹⁶ 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 et al¹⁷ was unbiased. It included 2 points to describe improvement, a neutral point, and 2 points to describe worsening. These 2 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 al¹⁵ found no difference between groups; Videler et al¹⁷ and Wallwork et al¹⁶ 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 3 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 al¹⁴ was an RCT containing 2 arms of treatment. 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 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 nonmacrolide comparator group.^{12,13} The retrospective study by Haruna et al¹³ 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 al¹² 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 nonmacrolide 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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FRCS, for use of the Cochrane ENT Disorders Group data collection form; Marisa L. Conte, BA, MLIS, for her assistance in data searching and study identification; Heather M. Hussey, MPH, for assistance with assessment of bias; and Peter Robertson, MPA, for assistance with obtaining studies. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author Contributions

Melissa A. Pynnonen, substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be published; **Giri Venkatraman**, substantial contributions to acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published; **Greg Davis**, substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published.

Disclosures

Competing interests: Melissa A. Pynnonen has provided 1 hour of consulting for K Storz. Greg Davis was an educational speaker for Stryker in 2011.

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