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INTRODUCTION

Chronic rhinosinusitis (CRS) with nasal polyps (CRSsNP) and CRS without nasal polyps (CRSwNP) represent multiple overlapping entities with various inflammatory patterns. Diversity in the pathogenesis of CRS associates 10 clusters by characteristic cytokines. Anti-inflammatory agents are the medical treatment for the long-term control of a variety of chronic inflamations.

Macrolides are acknowledged anti-inflammatory agents with immunomodulatory effects. They modulate neutrophilic action by suppression of lipopolysaccharide-induced neutrophil migration. The production of proinflammatory cytokines, such as interleukin (IL)-8 and tumor necrosis factor-alpha (TNF-α) is suppressed. In addition, they modulate the synthesis and secretion of mucus and alter mucus rheological properties, which results in effective clearance. Low-dose macrolides (LDMs) have been commonly utilized for treating upper airway diseases after its clinical effectiveness on diffuse panbronchiolitis was revealed.

Currently, long-term LDMs therapy in the management of CRS is controversial. Although recommended by international guidelines, the evidence supporting LDMs therapy is mixed. The first randomized controlled trial (RCT) showed clinical improvement, but another RCT showed no difference. In addition, there is no consensus among international guidelines on patient selection. The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS 2012) and the International Consensus Statement on Allergy and Rhinology recommend macrolides for both CRSsNP and CRSwNP subtypes. However, a systematic
review by Rudmik and Soler\textsuperscript{11} recommended macrolides for patients with CRSsNP but were against macrolides for patients with CRSwNP. Furthermore, Haxel et al.\textsuperscript{12} reported no differences between the patients with low and high serum IgE, although the EPOS 2012 suggested that patients with low serum IgE were macrolide responders. RCTs studying clinical effectiveness of LDMs are heterogeneous. The participants were different, not only in CRS subtypes (CRSwNP or CRSsNP) but also surgical status (without or with surgery). The types (14-membered lactone ring macrolides and 15-membered lactone ring macrolides), the dosages (half dose and very low dose), and the duration of treatment (less or longer than 12 weeks) of LDMs varied. We hypothesized that the anti-inflammatory and immunomodulatory effects of macrolides at optimal regimens should be effective for specific subgroups. This study aimed to assess the prognostic factors of LDMs therapy that may predict the favorable clinical outcomes by performing a meta-analysis and subgroup analyses.

**MATERIALS AND METHODS**

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-analyses statement.

**Eligibility Criteria**

RCTs studying the effects of LDMs therapy on patients with CRS were screened. The diagnostic criteria of CRS depended on individual studies. The inclusion criteria included the patients diagnosed with CRS by the study authors. The patients were 18 years old or older. Any type, dosage, and the LDMs given either after endoscopic sinus surgery (ESS) or without ESS were included. Any cointerventions were allowed if they were given to both arms of the study. The comparisons were 1) LDMs versus placebo, 2) LDMs plus standard treatment versus standard treatment, and 3) LDMs versus standard treatments. The outcomes were the Sino-Nasal Outcome Test (SNOT), symptom score, computed tomography (CT) score, endoscopy score, and gastrointestinal and cardiac adverse effects. Studies were excluded if the LDMs were given for a short-term duration of less than 6 weeks. The published RCTs in a language other than English were excluded.

**Information Sources and Search Strategy**

MEDLINE and Embase were searched using the terms: “sinusitis OR rhinosinusitis OR nasal polyp OR sinus surgery” AND “macrolide OR erythromycin OR clarithromycin OR roxithromycin OR azithromycin.” The last search was performed on March 17, 2018. References of the included studies and additional sources were searched to identify any published or unpublished trials that were missed.

**Study Selection Process**

The RCTs selection was performed independently by two reviewers (N.S. and C.S.). The reviewers independently screened the titles and abstracts based on the predetermined eligibility criteria. The full texts of the selected articles were reviewed. Any disagreements were resolved by consulting the corresponding author (K.SNIDVONGS), if necessary.

**Data Extraction**

Two review authors (K.SERESIRIKACHORN, W.C.) independently extracted data from the included studies using a predetermined data collection form. Six prognostic factors were collected including CRS subtype, serum IgE level, surgical status, membered lactone ring of macrolides, dose, and duration of treatment. The outcomes were collected at the end of the treatment. A change from the baseline with a standard deviation was extracted. A final score was extracted when a change from the baseline was not reported.\textsuperscript{13} Standard error, interquartile range and 95% confidence intervals (95% CI) were used when a standard deviation was not reported.\textsuperscript{13} Durability of outcomes improvement was collected if available.

**Risk of Bias in Individual Studies**

The risk of bias of the included studies was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{15} Five domains were assessed: 1) random sequence generation, 2) allocation concealment, 3) blinding of outcome assessment, 4) incomplete outcome data, and 5) selective reporting.

**Data Synthesis and Statistical Analysis**

Data were pooled for the meta-analysis. The mean difference (MD), standard mean difference (SMD) and 95% confidence interval (CI) were used for continuous data. The heterogeneity ($I^2$) was used to assess the discrepancies in the treatment effects between different trials. An $I^2$ of <40%, 40% to 60%, and >60% represented low, moderate, and substantial heterogeneity, respectively. A fixed-effects method was used when the statistical heterogeneity was low. A random-effects method was used when the statistical heterogeneity was high, to provide a more conservative estimate of the differences. Statistical assessments were performed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).\textsuperscript{14}

**Subgroup Analysis, Meta-regression, and Sensitivity Analysis**

Subgroup analyses by six prognostic factors were assessed. There were two subgroups of the CRS subtype: CRSwNP and CRSsNP. Studies with a mixed population were assigned to either CRSsNP or CRSwNP according to the majority of the population. There were two subgroups of the serum IgE level: high serum IgE (>100 IU/mL) and low serum IgE. There were two subgroups of the concurrent ESS: macrolides given with and without ESS. There were two subgroups of the dosage: half dose and less than half dose. The half doses of LDMs were defined as roxithromycin 150 mg once daily (OD), clarithromycin 500 mg OD, azithromycin 250 mg OD, and erythromycin 500 mg OD. There were two subgroups of the membered lactone ring: 14-membered lactone ring and 15-membered lactone ring. There were three subgroups of the duration of treatment: <12 weeks, 12 weeks, and longer than 12 weeks. Sensitivity analysis was performed by excluding studies with a high risk of bias at more than one domain. Meta-regression analyses would be performed in case the number of included studies was greater >10.

**RESULTS**

**Study Selection**

A total of 3,301 RCTs were screened (3,299 studies from electronic searches and two studies from manual searches). After screening, 3,269 studies were excluded. Twenty-two studies were removed after the full-text review. The reasons for exclusion are listed in Figure 1. Finally, 10 studies were included for qualitative synthesis\textsuperscript{8,9,12,15–21} and nine studies for quantitative synthesis.\textsuperscript{8,9,12,15,16,18–21} Characteristics of
the included studies are shown in Table I. A flowchart of the study retrieval and selection is presented in Figure 1.

**Participants**

Ten trials studied 608 participants, 50.3% were male, with the mean age of 43.9 years (nine studies). All patients were adults with CRS: CRSsNP (three trials), CRSwNP (three trials), and mixed subtypes of CRS (a major population of CRSwNP [three trials] and CRSsNP [one trial]). Two trials measured the serum IgE level at enrollment. Both studies had mixed populations of low and high serum IgE.

**Intervention**

Eight trials assessed the effects of 14-membered lactone ring macrolides. Of the eight trials, five trials used clarithromycin, two trials used erythromycin, and one trial used roxithromycin. Two trials assessed the effects of a 15-membered lactone ring macrolide, and both trials used azithromycin. Four trials used a half dose and six trials used less than a half dose.

Six trials gave LDMs without ESS. Of the four trials giving LDMs with concurrent ESS, one trial gave preoperative LDMs and three trials gave postoperative ESS.

Three trials gave LDMs with a duration of 8 weeks, and six trials for 12 weeks. One trial gave LDMs to one arm with a duration of 12 weeks with a 36% dropout rate, and another arm for 24 weeks with no dropouts. The 24-week duration was included for data extraction and analysis.

Six trials gave concomitant medication. Of the six trials, two trials gave concomitant nasal saline irrigation and intranasal steroid spray, three trials gave intranasal steroid spray, and one trial gave nasal saline irrigation.

**Comparisons**

Four trials compared LDMs therapy versus placebo. Four trials compared LDMs therapy plus standard treatment versus standard treatment.

![Flowchart of the study selection.](image-url)
LDms therapy to a standard treatment of intranasal steroid spray. One trial was excluded from quantitative synthesis because the LDms therapy was compared to herbal medicine, which was neither a placebo nor a standard treatment.8–17

Outcomes
Eight trials assessed the SNOT,8–12,15–18,20 seven trials assessed symptom scores,8,9,12,16,19–21 seven trials assessed endoscopy,8,12,16,17,19–21 and two trials assessed radiological scores.16,18 Nine trials reported gastrointestinal and cardiac adverse effects,8,9,12,15–20 and four trials reported data after the end of the treatment.8,9,12,19

Comparison: LDms Versus Placebo
The meta-analysis revealed no difference between the LDms and placebo in the improvement in 1) the SNOT (SMD = −0.23, 95% CI: −0.69 to 0.24),8,9,12,15 2) symptom score (SMD = −0.29, 95% CI: −1.46 to 0.89),8,12 and endoscopy score (SMD = −0.35, 95% CI: −0.71 to 0.00).8,12 There was no trial assessing the improvement in CT score. Heterogeneity was substantial for the SNOT (I² = 68%), symptom score (I² = 90%), and endoscopy score (I² = 0%). There was no heterogeneity (I² = 0%) for the endoscopy score.

Comparison: LDms Plus Standard Treatment Versus Standard Treatment
The cumulative meta-analysis revealed no difference between the LDms plus standard treatment and standard treatment in the improvement in 1) the SNOT (SMD = −0.52, 95% CI: −1.57 to 0.53),16,18,20 2) symptom score (SMD = −0.63, 95% CI: −1.42 to 0.16),16,19,20 3) endoscopy score (SMD = −1.85, 95% CI: −5.59 to 1.88),16,19,20 and 4) CT score (SMD = 0.15, 95% CI: −0.25 to 0.54),16,18 Heterogeneity was substantial for the SNOT (I² = 88%), symptom score (I² = 85%), endoscopy score (I² = 98%), and CT score. There was no heterogeneity (I² = 0%) for CT score.

Comparison: LDms Versus Placebo
There was only one RCT in this comparison.21 The results showed no difference between LDms and intranasal steroid spray in the improvement of symptom score (MD = 0.04, 95% CI: −0.56 to 0.64) and endoscopy score (MD = −0.49, 95% CI: −0.10 to 0.12). The SNOT and CT score were not assessed.21

Prognostic Factor: CRS Subtype
When subgroup analysis by CRS subtype was performed, the effects favored LDms over placebo in the improvement in the SNOT in patients with CRSsNP (SMD = −0.64, 95% CI: −1.01 to −0.27), but not in patients with CRSwNP (SMD = 0.18, 95% CI: −0.19 to 0.55). The subgroup difference was statistically significant (P = .009). The data are displayed in Figure 2. Likewise, the effects favored the LDms over placebo in the improvement in symptom score in patients with CRSsNP (MD = −0.89, 95% CI: −1.41 to −0.37), but not in patients with CRSwNP (SMD = 0.31, 95% CI: −0.21 to 0.83). The subgroup difference was statistically significant (P = .001). There was no difference between the two subgroups (P = .64) in endoscopy score.

Prognostic Factor: Serum IgE Level
Two RCTs measured serum IgE level at enrollment.8,12 The serum IgE level prognostic factor could not be assessed because both trials did not report data separately between patients with low and high serum IgE level.

Prognostic Factor: Concurrent ESS
Compared to placebo, LDms brought greater symptom improvement when given to patients without ESS (MD = 0.63, 95% CI: −0.10 to 0.33).21

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TABLE I.
Characteristics of Included Studies.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>CRS Subtype</th>
<th>Concurrent ESS</th>
<th>No. of Patients</th>
<th>No. of Macrolides</th>
<th>No. of Control</th>
<th>Macrolides</th>
<th>Dose (mg/d)</th>
<th>Control</th>
<th>Duration of Treatment (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallwork</td>
<td>2006</td>
<td>CRSsNP</td>
<td>Without ESS</td>
<td>61</td>
<td>29</td>
<td>35</td>
<td>Roxithromycin</td>
<td>150</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Videler</td>
<td>2011</td>
<td>Mixed (wNP)</td>
<td>Without ESS</td>
<td>60</td>
<td>29</td>
<td>31</td>
<td>Azithromycin</td>
<td>500/7</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Zeng</td>
<td>2011</td>
<td>CRSsNP</td>
<td>Without ESS</td>
<td>43</td>
<td>22</td>
<td>21</td>
<td>Clarithromycin</td>
<td>250</td>
<td>INCS</td>
<td>12</td>
</tr>
<tr>
<td>Jiang</td>
<td>2012</td>
<td>CRSsNP</td>
<td>Without ESS</td>
<td>53</td>
<td>27</td>
<td>26</td>
<td>Erythromycin</td>
<td>500</td>
<td>Herb</td>
<td>8</td>
</tr>
<tr>
<td>Peric</td>
<td>2014</td>
<td>CRSwNP</td>
<td>ESS:preoperative</td>
<td>80</td>
<td>40</td>
<td>40</td>
<td>Clarithromycin</td>
<td>250</td>
<td>No macrolide</td>
<td>8</td>
</tr>
<tr>
<td>Korkmaz</td>
<td>2014</td>
<td>CRSwNP</td>
<td>ESS:preoperative</td>
<td>44</td>
<td>22</td>
<td>22</td>
<td>Clarithromycin</td>
<td>250†</td>
<td>No macrolide</td>
<td>8</td>
</tr>
<tr>
<td>Varvyanskaya</td>
<td>2014</td>
<td>CRSwNP</td>
<td>ESS:postoperative</td>
<td>66</td>
<td>44</td>
<td>22</td>
<td>Clarithromycin</td>
<td>250</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Amali</td>
<td>2015</td>
<td>Mixed (wNP)</td>
<td>ESS:postoperative</td>
<td>66</td>
<td>22</td>
<td>44</td>
<td>Azithromycin</td>
<td>250</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Haxel</td>
<td>2015</td>
<td>Mixed (wNP)</td>
<td>ESS:postoperative</td>
<td>58</td>
<td>29</td>
<td>29</td>
<td>Erythromycin</td>
<td>250</td>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Deng</td>
<td>2018</td>
<td>Mixed (wNP)</td>
<td>Without ESS</td>
<td>74</td>
<td>38</td>
<td>36</td>
<td>Clarithromycin</td>
<td>250</td>
<td>No macrolide</td>
<td>12</td>
</tr>
</tbody>
</table>

*Study group received azithromycin 500 mg/d for 3 days during the first week followed by 500 mg/wk for 11 weeks.
†Study group received clarithromycin 1,000 mg/d during the first 2 weeks, followed by 250 mg/d for 6 weeks.
CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; Mixed (sNP) = mixed population with predominant without polyps; Mixed (wNP) = mixed population with predominant with polyps; INCS = Intranasal corticosteroids.
There was no difference between the two subgroups in symptom score improvement favored patients receiving a half dose of macrolides (SMD = 0.31, 95% CI: −0.27 to 0.83), but not the patients without ESS (SMD = 0.02, 95% CI: −0.46 to 0.51). The subgroup difference was statistically significant (P < .001). The improvement was not different between patients with and without ESS in symptom score (the patients without ESS, MD = −0.10, 95% CI: −0.59 to 0.38), and the patients with ESS (SMD = −0.94, 95% CI: −2.27 to 0.39; P = .25).

### Prognostic Factor: Dose of Macrolides

When subgroup analysis by dose of macrolides was performed, the effects favored the patients receiving a half dose of macrolides (SMD = −0.64, 95% CI: −1.01 to −0.27), over the patients receiving less than a half dose of macrolides (SMD = 0.18, 95% CI: −0.19 to 0.55; P = .002). The data are displayed in Figure 3. Likewise, the effects in symptom score improvement favored patients receiving a half dose of macrolides (MD = −0.89, 95% CI: −1.41 to −0.37), over the patients receiving less than a half-dose of macrolides (MD = 0.31, 95% CI: −0.21 to 0.83; P = .001). There was no difference between the two subgroups (P = .64) in endoscopy score.
Prognostic Factor: Membered Lactone Ring of LDMs

When subgroup analysis by membered lactone ring of LDMs was performed, the improvements in the SNOT were similar between the patients receiving a 14-membered lactone ring of LDMs (SMD = −0.24, 95% CI: −0.98 to 0.50), and the patients receiving a 15-membered lactone ring of LDMs (SMD = −0.21, 95% CI: −1.09 to 0.66; P = .96). The data are displayed in Figure 4.

Prognostic Factor: Duration of Treatment

When subgroup analysis by duration of LDMs treatment was performed, the effects in SNOT improvement...
favored patients receiving 24-week LDMs (SMD = –1.68, 95% CI: –2.40 to –0.95), over patients receiving 12-week LDMs (MD = –0.28, 95% CI: –0.77 to 0.21) and 8-week LDMs (MD = 0.36, 95% CI: –0.33 to 1.04; \( P = .002 \)). Likewise, the effects favored patients receiving 24-week LDMs in symptom improvement (MD = –1.65, 95% CI: –2.37 to –0.93), over patients receiving 12-week LDMs (MD = –0.10, 95% CI: –0.59 to 0.38) and 8-week LDMs (MD = –0.29, 95% CI: –0.73 to 0.15; \( P = .001 \)), and the effects favored patients receiving 24-week LDMs in endoscopy score (MD = –3.79, 95% CI: –4.85 to –2.73), over patients receiving 12-week LDMs (MD = 0.02, 95% CI: –0.46 to 0.51; \( P < .001 \)). The effects at 8 weeks in one RCT were not estimable. The improvement in CT score were similar between patients receiving 12-week LDMs (MD = 0.08, 95% CI: –0.40 to 0.56), and patients receiving 8-week LDMs (MD = 0.28, 95% CI: –0.40 to 0.96; \( P = .64 \)).

**Adverse Effects**

There were nine studies that reported gastrointestinal and cardiac adverse effects. \(^{8,9,12,15−20}\) LDMs produced greater gastrointestinal adverse effects (5%) when compared to other treatments (1.05%) (risk ratio: 3.52; 95% CI: 1.29 to 9.60). There was no cardiac adverse effect reported in any patients. The data are displayed in Table III.

**Durability of Outcomes Improvement**

There were four studies that reported data after the end of the treatment at the time point of 24 weeks. \(^{8,9,12,19}\) The meta-analysis revealed no difference between the LDMs and placebo in the improvement in 1) the SNOT \(^{8,9}\) (SMD = –0.28, 95% CI: –0.64 to 0.09) and 2) endoscopy score \(^{8,12}\) (SMD = –0.17, 95% CI: –0.53 to 0.18), and no difference between the LDMs plus standard treatment and standard treatment in the symptom score \(^{19}\) (MD = –0.06, 95% CI: –0.49 to 0.16). At the time point of 48 weeks, Peric et al. \(^{19}\) reported no difference between the LDMs plus standard treatment and standard treatment in the symptom score (MD = –0.17, 95% CI: –0.61 to 0.27).

**Risk of Bias of Included Studies**

The included studies had substantial selection bias for random sequence generation (60% low risk) and allocation concealment (50% low risk). They had modest risks in detection bias (70% low risk), attrition bias (80% low risk), and reporting bias (80% low risk).

**Sensitivity Analysis**

The sensitivity analysis was performed by excluding studies with multiple (more than one) high risks of bias from the meta-analysis. There were two RCTs excluded. \(^{19,20}\) Both RCTs compared LDMs plus standard treatment versus standard treatment. The results revealed two significant prognostic factors in that the LDMs were effective in SNOT improvement, which were CRSsNP and a half dose of LDMs, and three prognostic factors in symptom improvement, which were CRSsNP and a half dose of LDMs and LDMs therapy without ESS.

**Meta-regression Analysis**

Meta-regression analysis was not performed due to the limited number of included studies.
DISCUSSION

When compared to the controls, the overall effects of LDMs for treating CRS did not favor LDMs in the improvement of any outcomes. To date, there have been four meta-analyses assessing the effects of LDMs for treating CRS. Pynnönen et al. pooled data from two RCTs and showed no benefit of LDMs over placebo at the end of treatment. Head et al. extracted data from three RCTs. The meta-analysis included one RCT for each comparison, and each outcome showed no benefit of the LDMs therapy. The recent meta-analysis by Shen et al. included both randomized and nonrandomized controlled trials. Forest plots from the RCTs did not show the benefit of LDMs therapy.

Although the beneficial effects of LDMs therapy were not evident by meta-analyses, substantial heterogeneity was shown. When six predictive factors were assessed by our study, subgroup analyses revealed that LDMs were effective in a specific patient population or optimal treatment regimens. The CRS subtype and serum IgE were assessed in this study based on the mechanism of antineutrophilic action and the suppression of the production of IL-8 and TNF-α of the LDMs therapy. The findings from subgroup analyses showed that the LDMs therapy had beneficial effects in the improvement of the SNOT and symptom scores over placebo only in the patients with CRSsNP. These could be explained by the immunopathogenesis of CRSsNP driven by type 1/type 17 cytokines and the inflammatory pattern of neutrophilic/noneosinophilic inflammation. On the other hand, the CRSwNP associates with type 2 cytokines and high tissue eosinophilia. Thus, its immunopathogenesis may not respond to the immunomodulation pathway of macrolides. Serum IgE could not be assessed by our meta-analyses because the included studies did not report data separately between the patients with low and high serum IgE. The serum IgE level is acknowledged as a seromarker for type 2 in inflammation. On the other hand, the CRSwNP associates with type 2 cytokines and high tissue eosinophilia. Thus, its immunopathogenesis may not respond to the immunomodulation pathway of macrolides. Serum IgE could not be assessed by our meta-analyses because the included studies did not report data separately between the patients with low and high serum IgE. The serum IgE level is acknowledged as a seromarker for type 2 inflammation, and low serum IgE level has been recommended by the EPOS 2012 for identifying macrolide responders. However, clinical studies showed controversies. Wallwork et al. studied two subgroups of patients receiving roxithromycin: low (<200 IU/mL) and high serum IgE. Only the patients with low serum IgE showed improvement in the SNOT after treatment. It is worth noticing that the low IgE level defined by this study (<200 IU/mL) is greater than the general cut point of <100 IU/mL. Haxel et al. performed subgroup analysis and reported no difference in all outcomes between the patients with low (<100 IU/mL) and high serum IgE. Moreover, a recent study by Maniakas et al. gave azithromycin to patients who did not respond to postoperative budesonide irrigation, and found that the macrolide responders had higher mean serum IgE level (208 IU/mL) than the nonresponders (72 IU/mL). Recently, the local IgE production within the nose and paranasal sinuses in patients with CRS has been reported. Thus, the low serum IgE level may not be a good predictor to identify macrolide responders.

Subgroup analyses in this study showed no difference between the 14-membered ring and the 15-membered ring LDMs. The anti-inflammatory effects of LDMs that interfere with the cytokine production and inflammatory cell metabolism were revealed in the 14- and 15-membered ring but not 16-membered ring macrolides. The hydrophobic nature of the 14- and 15-membered lactone rings alters the biophysical properties of the cell membrane of the effector inflammatory cells. It interferes with the regulation of intracellular metabolic and transcriptional pathways involved in the inflammatory cascade. Thus, the low serum IgE level may not be a good predictor to identify macrolide responders.
the concentration-dependent reduction in IL-8. Duration of treatment is the other controversial issue. The included studies gave LDMs therapy for various durations of 8, 12, and 24 weeks. The findings from subgroup analyses revealed that the 24-week duration of LDMs therapy had greater benefits than other durations. The treatment of CRS aims to effectively control chronic inflammatory conditions of the paranasal sinuses. Neither corticosteroids nor LDMs therapy aims to cure the underlying etiologies. Thus, the duration of LDMs therapy should not be limited to 12 weeks. Longer duration of LDMs therapy may achieve better long-term disease control by the current anti-inflammatory and immunomodulatory effects.

Subgroup analyses by concurrent ESS in this study showed mixed results. Patients receiving LDMs without ESS had greater improvement in symptoms than placebo. However, the patients receiving LDMs with concurrent ESS had greater improvement in the SNOT and endoscopy score. After removing the low-quality studies to perform sensitivity analysis, the patients without ESS had a greater symptom score improvement. However, the effect was too small (0.89) to be clinically meaningful. On the other hand, the effects of the SNOT improvement (1.68) and endoscopy score improvement (3.79) found in patients with concurrent ESS were larger. Overall, the findings suggested the modest beneficial effect of LDMs therapy without ESS was inferior to corticosteroids and ESS.

Thus, the LDMs therapy should not be the first-line treatment for patients with CRS. Among the studies of LDMs with concurrent ESS, Peric et al.19 did not find any benefit of preoperative LDMs. The LDMs therapy after ESS for long-term control of chronic inflammatory conditions of paranasal sinuses, which cannot be managed by surgery, is clinically meaningful and more practical.

To the best of our knowledge, this study is the first meta-analysis assessing prognostic factors that predict the success of LDMs therapy in patients with CRS. The findings suggested that LDMs therapy provided clinical effectiveness to patients with CRSsNP. LDMs therapy should be an option for some groups of patients. When LDMs are considered, a half-dose of LDMs for 24 weeks duration is recommended.

The limitation of this study is that the 10 included studies in this meta-analysis had multiple comparisons with several treatment outcomes. When subgroup analyses were performed, the number of patients in each subgroup may not have had enough power to see a statistically significant difference. The heterogeneity was substantial in some meta-analyses. Bias among the included studies was demonstrable.

CONCLUSION

Although overall beneficial effects were not demonstrated, LDMs with appropriate treatment regimens may provide clinical benefits in disease-specific quality of life, symptoms, endoscopy, and radiology to a specific patient population. The findings from meta-analyses and subgroup analyses suggested that the LDMs should be clinically effective in patients with CRSsNP. When LDMs are administered, a half-dose of macrolides for 24 weeks duration is suggested. Favorable outcomes may be achieved in both patients receiving macrolides with and without ESS.

Acknowledgments

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