Predictive factors for identifying macrolide responder in treating chronic rhinosinusitis

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การหาตัวแปรพยากรณ์ในการระบุกลุ่มผู้ป่วยที่ตอบสนองต่อการรักษาด้วย macrolide ในการรักษาโรคไซนัสอักเสบเรื้อรัง

นายขจร เสรีศิริขจร

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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ขจร เสรีศิริขจร : การหาตัวแปรพยากรณ์ในการระบุกลุ่มผู้ป่วยที่ตอบสนองต่อการรักษาด้วย macrolide ในการรักษาโรคไซนัสอักเสบเรื้อรัง. (Predictive factors for identifying macrolide responder in treating chronic rhinosinusitis) อ.ที่ปรึกษาหลัก : รศ. นพ.กรเกียรติ์ สนิทวงศ์

ภูมิหลัง: จากคุณสมบัติของยาแมคโครไลด์ขนาดต่ำซึ่งมีฤทธิ์ลดการอักเสบแบบนิวโทรฟิล ทำให้ไม่เหมาะกับการรักษาไซนัสอักเสบเรื้อรังชนิดที่มีการอักเสบแบบอีโอซิโนฟิล ดังนั้นจึงควรมีการหาปัจจัยทำนายในการพยากรณ์การตอบสนองต่อการรักษาด้วยยาแมคโครไลด์ขนาดต่ำ รวมถึงจัดกลุ่มปัจจัยทำนายนี้เพื่อนำไปใช้เป็นหลักเกณฑ์ในการเลือกใช้ยาแมคโครไลด์ขนาดต่ำในการรักษาไซนัสอักเสบเรื้อรัง

วิธีการศึกษา: การศึกษาจากเหตุไปหาผลแบบไปข้างหน้าได้ศึกษาในผู้ป่วยไซนัสอักเสบเรื้อรังผู้ใหญ่ มีการเก็บข้อมูลอาการ, คะแนนค่าซีทีสแกนไซนัส, คะแนนอาการทางจมูก และแบบประเมินคุณภาพชีวิต ผู้ป่วยทุกรายได้รับยา roxithromycin 150 มิลลิกรัม วันละครั้ง ร่วมกับการล้างจมูกเป็นเวลา 12 สัปดาห์ คะแนนอาการทางจมูกจะได้รับการประเมินทุกครั้งที่นัดหมาย ถ้าคะแนนมากกว่า 7 ในแต่ละการนัดหมาย ผู้ป่วยจะหยุดการรักษาและจัดว่าเป็นกลุ่มที่ไม่ตอบสนองต่อยาแมคโครไลด์ขนาดต่ำ ปัจจัยทำนายจะถูกเก็บข้อมูลก่อนการรักษา เมื่อสิ้นสุดการรักษาผู้ป่วยจะถูกจำแนกเป็นกลุ่มที่ตอบสนองหรือไม่ตอบสนองต่อยาแมคโครไลด์ขนาดต่ำ

ผลการศึกษา: ผู้ป่วย 100 ราย (อายุเฉลี่ย 47.35 ± 14.13 (SD) ปี, 45% ผู้ชาย) ที่เป็นไซนัสอักเสบเรื้อรังเข้าร่วมในการศึกษานี้ โดยพบว่ามี 29 รายตอบสนองต่อยาแมคโครไลด์ขนาดต่ำ พบว่ามีเพียง 2 ปัจจัยทำนายที่สามารถพยากรณ์การตอบสนองต่อยาแมคโครไลด์ขนาดต่ำอย่างมีนัยสำคัญทางสถิติ คือ total IgE < 4.76 kU/l ในน้ำมูก (Odd Ratio: 3.06, 95%CI: 1.16 - 8.06) และค่า eosinophils < 3.7%ในเลือด (Odd Ratio:2.45, 95%, CI 1.01 – 5.93) นอกจากนี้จากการวิเคราะห์การถดถอยโลจิสติคแบบหลายตัวแปรพบว่า มีเพียง total IgE < 4.76 kU/l ในน้ำมูกเท่านั้นที่มีความสัมพันธ์อย่างเป็นอิสระกับการตอบสนองต่อยาแมคโครไลด์ขนาดต่ำ (Odd Ratio: 3.06, 95%CI: 1.16 - 8.06)

ผลสรุป: ค่า total IgE < 4.76 kU/l ในน้ำมูกสามารถใช้เป็นปัจจัยทำนายการตอบสนองต่อการรักษาด้วยยาแมคโครไลด์ขนาดต่ำในผู้ป่วยไซนัสอักเสบเรื้อรัง

สาขาวิชา	เวชศาสตร์คลินิก	ลายมือชื่อนิสิต .....
ปีการศึกษา	2563	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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KEYWORD: macrolides, sinusitis, nasal polyps, anti-inflammatory, total IgE

Kachorn Seresirikachorn : Predictive factors for identifying macrolide responder in treating chronic rhinosinusitis. Advisor: Assoc. Prof. KORNKIAT SNIDVONGS, Ph.D.

Background: A low-dose macrolide (LDM) has antineutrophilic activity, so they should not work for eosinophilic inflammation. Clinical predictors are required to select favorable patients for LDM therapy appropriately. This study aims to assess individual predictive factors and propose suitable multiple predictive factors for identifying a macrolide responder in treating CRS.

Methodology: Prospective cohort study was done in adult CRS patients. Clinical data collection, Lund-Mackay CT score, visual analog scale (VAS), and sino-nasal outcome test 22 (SNOT-22) were assessed. Patients received 150 mg of roxithromycin once daily plus saline irrigation for 12 weeks. VAS was evaluated at every visit. If the patients had total nasal symptoms VAS > 7 at any visit, they were defined as macrolides non-responders. Nine predictors for macrolide responders were assessed. At the end of treatment, the patients were defined as either macrolide responders or non-responders.

Results: 100 patients (mean–±SD age 47.35 ± 14.13 years, 45% male) with CRS were included. 29 patients met the criteria of macrolide responders. Only local total IgE < 4.76 kU/l (OR: 3.06, 95%CI: 1.16 - 8.06) and serum eosinophils < 3.7% (OR:2.45, 95%, CI 1.01 – 5.93) showed a statistically significant association with macrolide response. Moreover, in a multivariate regression model, local total IgE was the only variable that maintained an independent association with macrolide response (OR: 3.06, 95%CI: 1.16 - 8.06).

Conclusions: Low local total IgE (< 4.76 kU/l) from nasal secretion may be a suitable predictor for identifying macrolides responders in treating chronic rhinosinusitis with LDM.

Field of Study:	Clinical Sciences	Student's Signature .....
Academic Year:	2020	Advisor's Signature .....

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Kachorn Seresirikachorn

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CHAPTER 1 INTRODUCTION

1.1 Introduction

Chronic rhinosinusitis (CRS) represents multiple overlapping entities with various inflammatory patterns. Traditionally, CRS with nasal polyps (CRSwNP) is acknowledged Th2-skewed eosinophilic inflammation with elevated levels of IL-5, IgE, Eotaxins and Eosinophilic cationic protein (ECP). In contrast, CRS without nasal polyps (CRSsNP), is acknowledged Th1/Th17-skewed neutrophilic inflammation with elevated levels of interferon-γ (IFNγ), transforming growth factor-β (TGFβ), IL-17, Myeloperoxidase (MPO), IL-6, IL-8, IL-1β[1-3].In comprehensive medical treatment for CRS, anti-inflammatory drugs become the primary medical therapy. CRSwNP is acknowledged steroid-responsive, both systemically and topically administered. Doxycycline with anti-MMP9 property should play a role in controlling CRSwNP inflammation[4]. CRSsNP is acknowledged neutrophilic inflammation; therefore, macrolide with antineutrophillic activity play a role.

However, randomized controlled trials (RCT) assessing the effectiveness of macrolide for treating CRS do not show evidence supporting the traditional concept. The first RCT by Wallwork et al. found no difference in SNOT-20 between macrolide (roxithromycin) and placebo when they followed the patients with CRSsNP at 24 weeks timepoint[5]. The second RCT by Videler et al. found no difference in SNOT-22 between macrolide (azithromycin) and placebo when they followed the patients with CRSsNP and CRSwNP at 12 weeks timepoint[6]. The third RCT by Varvyanskaya et al. found macrolide (Clarithromycin) beneficial in SNOT-20 when compared with placebo but in patients with CRSwNP, instead of CRSsNP[7]. The fourth RCT by Haxel et al. found no difference in SNOT-20 between macrolide (erythromycin) and placebo when they followed the patients with CRSsNP and CRSwNP at 12 weeks timepoint[8]. These findings are in contrast to the traditional principle of how macrolide should work in CRS with Th1/Th17 inflammation.

Nevertheless, some beneficial effects were shown by these studies, such as nasal endoscopy[8]. Besides, the first RCT by Wallwork et al. found roxithromycin beneficial in SNOT-20 after treatment of 12 weeks time point[5]. Controversy on using long term macrolide therapy, therefore,

is still debating. Considering the mechanism of actions, macrolide should work not all patients with CRS but should work in specific subgroups. Appropriate predictive factors should enable clinicians to identify these responders.

There is a controversy about how we select a patient for macrolide therapy among guidelines. European position paper on rhinosinusitis and nasal polyps 2012 (EPOS 2012) recommends long term (>12 weeks) macrolide therapy in a patient with CRSsNP with low serum IgE[9]. A systematic review and meta-analysis by Rudmik et al. recommend macrolide therapy for a patient with CRSsNP without measuring serum IgE level[10]. International Consensus Statement on Allergy and Rhinology (ICAR) recommends macrolide therapy as an option in a patient with both CRSsNp and CRSwNP[11].

While guidelines recommend macrolide for a patient with CRSsNP, beneficial effects were shown for a patient with CRSwNP in the RCT by Varvyanskaya et al. [7]. The phenotype of the nasal polyp may not truly represent the endotype of Th2 inflammation, therefore might not be a good predictive factor for not giving macrolide therapy. A cross-sectional study by Snidvongs et al. found that high tissue eosinophilia (>10 per high-power field (HPF)) was more prominent in polyps (84%) but was also seen in nonpolyp patients (19%)[12]. Soler et al. found that both patients with CRSsNP and CRSwNP can have Th2 inflammation with high tissue eosinophilia. Patients in the group of eosinophilia but without polyps have the worst life quality and worse than eosinophilia with polyps[13]. Zhang et al. found that Asian nasal polyps have the characteristics of Th1/Th17 inflammation which are different from polyps of white patients[3]. These findings are in contrast to the traditional concept that CRSsNP represents Th1 inflammation and CRSwNP represents Th2 inflammation. In other words, the endotype of Th1/Th17 might be a better indicator of inflammatory pattern and macrolide responder than the phenotype of CRSsNP.

Nowadays, there is a growing body of evidence showing local IgE production in rhinosinusitis and an association between increased levels of total local IgE, specific local IgE, and eosinophilic inflammation in nasal polyps is revealed[14]. Moreover, specific local IgE can be present in patients with negative systemic allergy testing, including serum IgE measurements[15]. Although local IgE production can be the effect of stimulation with allergens in atopic nasal polyp patients, local IgE

is also present in non-atopic patients[1]. In other words, elevated local IgE levels may result from other pathways as well. Therefore, the recommendation of measuring serum IgE as a predictive marker for taking macrolide by EPOS2012[9] might not be suitable. When IgE is produced locally in rhinosinusitis, local IgE should be a more suitable predictive marker.

To date, there is no accurate predictive factor in predicting CRS patients responsive to macrolide therapy. Therefore, this study aims to assess individual predictive factor and propose a group of suitable predictive factors for identifying macrolide responder in treating CRS. The hypothesis is a criterion composing of multiple factors better predict macrolide responder in treating CRS compared to one individual factor. Absence of nasal secretion IgE should be one of the criteria for identifying macrolide responder in treating CRS.

Literature Review

Pathophysiology of CRS

CRS is a disease with inflammation of nasal and sinus mucosa, and the symptoms exist more than 12 weeks without recovering period. The pathophysiology of CRS is not known. Harvey et al. proposed a theory describing the pathophysiology of CRS and three major contributing factors, including (1) mucosal inflammation (2) mucociliary dysfunction (3) local microbial community. These 3 factors affect each other. When there is mucosal inflammation, it would cause mucociliary dysfunction and bring easier infection. When there is mucociliary dysfunction, it will cause an accumulation of mucus, which causes mucosal inflammation and colonization of various microbes[16].

Mechanism of action of macrolide

Long term macrolide therapy (>12 weeks) is a medical therapy for treating CRS. A systematic review and meta-analysis by Rudmik et al. included 29 studies. Evidence has been shown that macrolide inhibits NF-kB pathway, blocks binding to TGFβ receptor, inhibits neutrophil migration and promotes neutrophil apoptosis. All of these mechanisms reduce neutrophilic inflammation and IL-8[10]. Considering pathophysiology of CRS with the three major contributing

factors, macrolide has effects across all three interacting processes: the ability to modulate the neutrophilic immune response, direct activity on bacteria, antibiofilm properties, and changes to mucus rheology and production[16].

Effectiveness of macrolide for treating CRS

Controversy on the effectiveness of macrolide therapy is found among four RCTs. Studies are reporting both similar effects and beneficial effects after giving macrolide when compared to placebo.

The first RCT by Wallwork et al. 2006 randomized patients with CRSsNP to receive either macrolide (roxithromycin) or placebo for 12 weeks. It was found that roxithromycin-treated patients showed significant improvements in saccharine transit time (P< .01), nasal endoscopic scoring (P<.01), SNOT-20 scoring (P<.01) after treatment. When they followed the patients with CRSsNP at 24 weeks time point, there was no difference between groups. In this study, middle meatal swabs performed before and after treatment failed to show any macrolide-resistant organisms[5].

In 2011, Videler et al. randomized patients with CRSsNP and CRSwNP to receive either macrolide (azithromycin) or placebo for 12 weeks. It was found that there was no significant difference between the AZM and the placebo groups in every outcomes[6].

In 2014, Varvyanskaya et al. randomized postoperative patients with CRSwNP to receive either 12 weeks macrolide (clarithromycin) or 24 weeks macrolide (clarithromycin) or placebo. It was found that long-term low-dose clarithromycin 250 mg/day controlled eosinophilic inflammation, improved SNOT-20, CT, and nasal endoscopy and prevented early relapse of NP after FESS[7].

In 2015, Haxel et al. randomized patients with CRSsNP and CRSwNP to receive either macrolide (erythromycin) or placebo for 12 weeks. It was found that no difference in SNOT-20 between macrolide (erythromycin) and placebo. However, nasal endoscopy score showed a statistically significant improvement in the erythromycin group compared to the placebo group[8].

Endotype and phenotype of CRS

Kern et al. 2008 found that patients with CRSsNP had outstanding inflammatory cytokines which are interferon-γ (IFNγ) and transforming growth factor-β (TGFβ), which represent Th1 inflammation. As for CRSwNP, there are outstanding inflammatory cytokines which are Eotaxins, Eosinophilic cationic protein, IL 5, IgE which represent Th2 inflammation[2]. Zhang et al. 2008 studied 47 Belgians and 58 Chinese patients and found that Asian nasal polyps are different from white patients polyps having the characteristics of Th1/Th17 inflammation[3].

Soler et al.2010 studied the quality of life of 102 CRS patients after endoscopic sinus surgery. When categorized by endotype, it was found that patients in the group of eosinophilia but without polyps had the worst life quality and worse than eosinophilia with polyps[13].

Snidvongs et al. 2012 assessed histopathology of 51 patients with CRS and found that high tissue eosinophilia (>10 per high-power field (HPF)) was more prominent in polyps (84%) but was also seen in nonpolyp patients (19%)[12].

Local IgE production in CRS

Bachert et al. reviewed the literature and proposed that there is local IgE production in the nasal mucosa. There is an association between increased levels of total local IgE, specific local IgE, and eosinophilic inflammation in nasal polyps, which may be of relevance in the pathophysiology of nasal polyposis[14].

Baba et al. 2014 studied local IgE in 44 Japanese patients with CRSwNP and found that the concentrations of total local IgE and number of IgE-positive cells were significantly higher in the eosinophilic polyps compared with control and non-eosinophilic polyps[17].

Suh et al. 2004 studied 30 patients with CRSwNP assessing total local IgE and HDM-specific local IgE in nasal polyp tissue in patients with strong and weak systemic hypersensitivity, and controls. They found a high IgE-level in both atopic groups, suggesting local IgE production regardless of systemic atopy[18].

Els De Schryver et al. reviewed the literature concerning mechanism in creating local IgE in CRSwNP. There are two pathways in local IgE production in CRSwNP. In the first pathway, dendritic cells of the skin and mucosa process aeroallergens deposit on the mucosa, and subsequently they present antigens to T cells. T helper two cells release their mediators upon recognition of antigens presented by antigen-presenting cells. The Th2 cytokines IL4, IL13, and CD40L, induce selective somatic recombination of immunoglobulin heavy chain regions in B cells before maturation into IgE-producing plasma cells. IL5 stimulates eosinophil growth and differentiation. Alternatively, IgE is produced by stimulating innate lymphoid cells to release IL4, IL5, and IL13. The cytokines IL25 and IL33 induce IgE-mediated inflammation by stimulating a non-T cell source to produce IL4, IL5, and IL13, namely innate lymphoid cells (ILC)[1].

Lam et al. 2013 studied 37 patients with CRS and found that IL-25, IL-33, and eotaxin-3 were significantly overexpressed in CRSwNP patients with greater severity in terms of symptoms, endoscopy and CT compared to CRSsNP patients and controls[19].

Lam et al. 2015 studied 39 patients with CRS and found that IL-25 and IL-33 overexpression was observed in eosinophilic CRS. The release of these cytokines by dysfunctional endothelium may perpetuate the eosinophilic inflammation in CRS[20]. From both studies by Lam et al., it showed evidence of creating local IgE from another pathway apart from Th2 inflammation.

EPOS 2012 recommended the use of long term (>12 weeks) macrolide guided by the phenotype of CRSsNP with low serum IgE[9]. This recommendation is based on the study of Wallwork et al. 2006 that divided patients with CRSsNP into two subgroups; low serum IgE and high serum IgE. It was found that macrolide more significant reduced saccharine transit time, nasal endoscopic scoring, SNOT-20 scoring and IL-8 in low serum IgE subgroups[5].

Predictive factors to predict macrolide responders

To date, there is no adequate study investigating appropriate predictive factors for identifying macrolide responder for treating chronic rhinosinusitis. Evidence is not yet shown.

In 2009, Harvey et al. suggested that patients without atopy or eosinophilia are more likely to respond to macrolide therapy. The presence of high IgE (>200–250 U/mL), peripheral eosinophilia, or nasal eosinophilia should be poor prognostic factors[16]. However, this recommendation is not data-driven.

In 2012 EPOS recommended the use of long term (>12 weeks) macrolide guided by the phenotype of CRSsNP with low serum IgE[9]. There is no clear evidence supporting this recommendation.

In 2016 International Consensus Statement on Allergy and Rhinology(ICAR) recommended using macrolide as an option in both CRSsNP and CRSwNP[11].This is base on the systematic review and meta-analysis of Rudmik et al. 2015[10]. There is no clear evidence supporting this recommendation.

1.2 Research question

What are predictive factors for identifying macrolide responder in treating chronic rhinosinusitis?

1.3 Published articles related to the thesis

1. Factors of success of low-dose macrolides in chronic sinusitis: systematic review and meta-analysis

2. Low-dose macrolides for treating pediatric rhinosinusitis: a retrospective study and literature review

3. Predictive factors for identifying macrolide responder in treating chronic rhinosinusitis

CHAPTER 2 FACTORS OF SUCCESS OF LOW-DOSE MACROLIDES IN CHRONIC SINUSISITIS: SYSTEMETIC REVIEW AND META-ANALYSIS

2.1 Introduction

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) represent multiple overlapping entities with various inflammatory patterns[9]. Diversity in pathogenesis of CRS associates with a wide spectrum of immunologic profiles and expressions of various Th cell types and simultaneous expression of multiple Th cell types has been shown in some patients[21]. Thus, heterogeneity among patients with CRS is so remarkable that patients may be classified into 10 clusters by characteristic cytokines[22]. Anti-inflammatory agents are the medical treatment for the long-term control of a variety of chronic inflammations.

Macrolides are acknowledged anti-inflammatory agents with immunomodulatory effects[23, 24]. 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[25]. In addition, they modulate the synthesis and secretion of mucus and alter mucus rheological properties which results in effective clearance[25]. Low-dose macrolides (LDM) have been commonly utilized for treating upper airway diseases after its clinical effectiveness on diffuse panbronchiolitis was revealed[26].

Currently, the long-term LDM therapy in the management of CRS is controversial. Although recommended by international guidelines, the evidence supporting the LDM therapy is mixed. The first randomized controlled trial (RCT) showed clinical improvement[5], but the other RCT showed no difference[6]. In addition, there is no consensus among international guidelines on patient selection. The European position paper on rhinosinusitis and nasal polyps 2012 (EPOS 2012)[9] and the International Consensus Statement on Allergy and Rhinology (ICAR)[11] recommend macrolides for both CRSsNP and CRSwNP subtypes. However, a systematic review by Rudmik et al[10]. recommended macrolides for patients with CRSsNP but against the patients with CRSwNP. Besides, Haxel et al[8] reported no differences between the patients with low and high serum IgE, although the EPOS 2012 suggested that the patients with low serum IgE were

macrolide responders. RCTs studying clinical effectiveness of LDM are heterogenous. 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 LDM 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 LDM therapy that may predict the favorable clinical outcomes by performing meta-analysis and subgroup analyses.

2.2 Material and Methods

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria

RCTs studying the effects of LDM 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 LDM given either after endoscopic sinus surgery (ESS) or without ESS were included. Any co-interventions were allowed if they were given to both arms of the study. The comparisons were 1) LDM versus placebo, 2) LDM plus standard treatment versus standard treatment, and 3) LDM 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 LDM was 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 17 March 2018. References of the included studies and additional sources were searched for identifying any missing published or unpublished trials.

Study Selection Process

The RCTs selection was performed independently by two reviewers (NS and CS). 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 (KSn), if necessary.

Data Extraction

Two review authors (KSe, WC) 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 (SD) was extracted. A final score was extracted when a change from the baseline was not reported[13]. Standard error, interquartile range and 95% confidence intervals (95% CI) were used when a standard deviation was not reported[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[27]. 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% 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 less than 40, 40–60%, and greater than 60% represented low, moderate, and substantial heterogeneity, respectively. A fixed-effect method was used when the statistical heterogeneity was low. A random-effect 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[28] (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Subgroup analysis, meta-regression and sensitivity analysis

Subgroup analyses by six prognostic factors were assessed. There were two subgroups of the CRS subtype: CRSwNP, CRSsNP. Studies with a mixed population were assigned to either CRSsNP or CRSwNP according to the majority of the population. There were 2 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 LDM were defined as roxithromycin 150 mg 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: less than 12 weeks, 12 weeks and longer than 12 weeks. Sensitivity analysis was performed by excluding studies with high risk of bias at more than one domain. Meta-regression analyses would be performed in case that the number of included studies was greater than ten.

2.3 Results

Study Selection

A total of 3,301 RCTs were screened (3,299 studies from electronic searches and 2 studies from manual searches). After screening, 3269 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[5-8, 29-34] and 9 studies for quantitative synthesis[5-8, 29, 30, 32-34]. Characteristics of the included studies are shown in Table 1. A flow chart of the study retrieval and selection is presented in Figure 1.

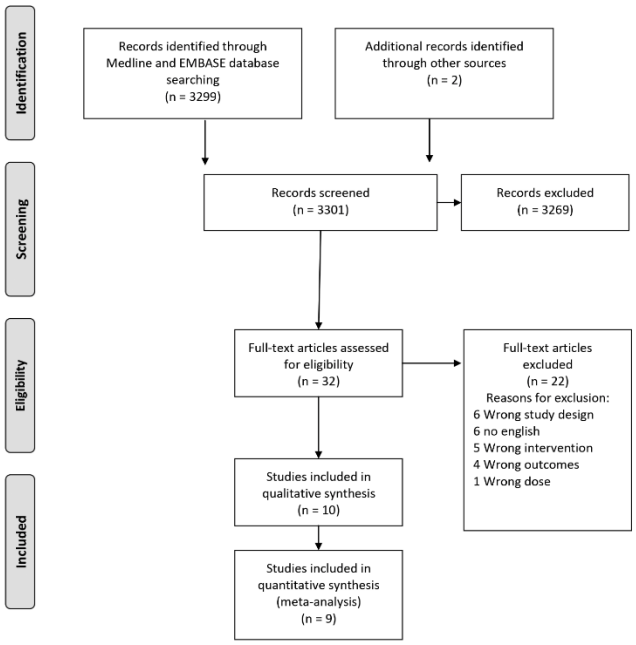

Figure 1 Flow diagram of study selection

TABLE I.
Characteristics of Included Studies.

First Author	Year	CRS Subtype	Concurrent ESS	No. of Patients	No. of Macrolides	No. of Control	Macrolides	Dose (mg/d)	Control	Duration of Treatment (wk)
Wallwork	2006	CRSsNP	Without ESS	64	29	35	Roxithromycin	150	Placebo	12
Videler	2011	Mixed (wNP)	Without ESS	60	29	31	Azithromycin	500/7*	Placebo	12
Zeng	2011	CRSsNP	Without ESS	43	22	21	Clarithromycin	250	INCS	12
Jiang	2012	CRSsNP	Without ESS	53	27	26	Erythromycin	500	Herb	8
Peric	2014	CRSwNP	ESS:preoperative	80	40	40	Clarithromycin	500	No macrolide	8
Korkmaz	2014	CRSwNP	Without ESS	44	22	22	Clarithromycin	250†	No macrolide	8
Varvyanskaya	2014	CRSwNP	ESS:postoperative	66	44	22	Clarithromycin	250	No macrolide	24
Amali	2015	Mixed (sNP)	ESS:postoperative	66	22	44	Azithromycin	250	Placebo	12
Haxel	2015	Mixed (wNP)	ESS:postoperative	58	29	29	Erythromycin	250	Placebo	12
Deng	2018	Mixed (wNP)	Without ESS	74	38	36	Clarithromycin	250	No macrolide	12

*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.

Table 1 Characteristics of included studies

Participants

Ten trials studied 608 participants, 50.3% were male with the mean age of 43.9 years (9 studies[6-8, 29-34]). All patients were adult with CRS: CRSsNP (3 trials[5, 31, 34]), CRSwNP (3 trials[7, 32, 33]) and mixed subtypes of CRS (a major population of CRSwNP (3 trials[6, 8, 30]) and CRSsNP (one trial[29]). Two trials measured the serum IgE level at enrollment[5, 8]. Both studies had mixed population of low and high serum IgE.

Intervention

Eight trials assessed the effects of 14-membered lactone ring macrolides[5, 7, 8, 30-34]. Of the eight trials, five trials used clarithromycin[7, 30, 32-34], two trials used erythromycin[8, 31] and one trial used roxithromycin[5]. Two trials assessed the effects of 15-membered lactone ring macrolide, both trials used azithromycin[6, 29]. Four trials used half dose[5, 29, 31, 33] and six trials used less than half dose[6-8, 30, 32, 34]. Six trials gave LDM without ESS[5, 6, 30-32, 34]. Of the four trials giving LDM with concurrent ESS[7, 8, 29, 33] , one trial gave pre-operative LDM[33] and three trials gave postoperative ESS[7, 8, 29].Three trials gave LDM with a duration of 8 weeks[31-33] and six trials for 12 weeks[5, 6 8, 29 30, 34]. One trial gave LDM to one arm with a duration of 12 weeks with 36% dropout and another arm for 24 weeks with no dropout[7]. 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[8, 29], three trials gave intranasal steroid spray[7, 30, 32] and one trial gave nasal saline irrigation[6].

Comparisons

Four trials compared LDM therapy versus placebo[5, 6, 8, 29]. Four trials compared LDM therapy plus standard treatment versus standard treatment[7, 30, 32, 33]. One trial compared LDM therapy to a standard treatment, intranasal steroid spray[34]. One trial was excluded from quantitative synthesis because the LDM therapy was compared to herbal medicine which was neither a placebo nor a standard treatment[31].

Outcomes

Eight trials assessed Sino-nasal outcome test (SNOT)[5-8, 29-32]. Seven trials assessed symptom score[5-8, 30, 33, 34], seven trials assessed endoscopy[5, 7, 8, 30, 31, 33, 34], two trials assessed radiological score[30, 32] and nine trials reported gastrointestinal and cardiac adverse effects[5-8, 29-33] and four trials reported data after the end of the treatment[5, 6, 8, 33].

Overall effects of LDM therapy

The data of findings from meta-analyses and subgroup analysis are displayed in Table 2.

Comparison: LDM versus Placebo

The meta-analysis revealed no difference between the LDM and placebo in the improvement in (1) SNOT (SMD -0.23, 95%CI -0.69 to 0.24)[5, 6, 8, 29], (2) symptom score (SMD -0.29, 95%CI -1.46 to 0.89)[5, 8], and endoscopy score (SMD -0.35, 95%CI -0.71 to 0.00) [5, 8]. There was no trial assessing the improvement in CT score. Heterogeneity was substantial for SNOT (I^2=68%), symptom score (I^2=90%). There was no heterogeneity (I^2=0%) for endoscopy score.

Comparison: LDM plus standard treatment versus standard treatment

The cumulative meta-analysis revealed no difference between the LDM plus standard treatment and standard treatment in the improvement in (1) SNOT (SMD -0.52, 95%CI -1.57 to 0.53)[7, 30, 32], (2) symptom score (SMD -0.63, 95%CI -1.42 to 0.16)[7, 30, 33], (3) endoscopy score (SMD -1.85, 95%CI -5.59 to 1.88) [7, 30, 33] and (4) CT score (SMD 0.15, 95%CI -0.25 to 0.54)[30, 32]. Heterogeneity was substantial for SNOT (I^2=88%), symptom score (I^2=85%), endoscopy score (I^2=98%). There was no heterogeneity (I^2=0%) for CT score.

Comparison: LDM versus standard treatment

There was only one RCT in this comparison[34]. The results showed no difference between LDM 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 Sinonasal outcome test and CT score were not assessed[34].

TABLE II.
Summary of Findings From Meta-analyses and Subgroup Analyses.

Prognostic Factors	Comparison	Outcomes			
		QOL Score	Symptom Score	Endoscopy Score	CT Score
1. CRS subtype 1.1 CRSwNP 1.2 CRSsNP	LDMs vs. placebo	Favor CRSsNP, SMD −0.64 (−1.01, −0.27)	Favor CRSsNP, SMD −0.89 (−1.41, −0.37)	N/D	N/A
	LDMs plus Standard treatment vs. standard treatment	N/D	N/D	N/D	N/D
	LDMs vs. standard treatment	N/A	N/A	N/A	N/A
2. Serum IgE	LDMs vs. placebo	N/A	N/A	N/A	N/A
2.1 low serum IgE 2.2 high serum IgE	LDMs plus standard treatment vs. standard treatment	N/A	N/A	N/A	N/A
	LDMs vs. standard treatment	N/A	N/A	N/A	N/A
3. Concurrent ESS 3.1 LDMs w/o ESS 3.2 LDMs with ESS	LDMs vs. placebo	N/D	Favor LDMs without ESS, SMD −0.89 (−1.41, −0.37)	N/D	N/A
	LDMs plus standard treatment vs. standard treatment	Favor LDMs with ESS, SMD −1.68 (−2.40, −0.95)	N/D	Favor LDMs With ESS, SMD −3.79 (−4.85, −2.73)	N/D
	LDMs vs. standard treatment	N/D	N/D	N/D	N/D
4. Dose 4.1 Half dose 4.2 Less than half dose	LDMs vs. placebo	Favor half dose, SMD −0.64 (−1.01, −0.27)	Favor half dose, SMD −0.89 (−1.41, −0.37)	N/D	N/A
	LDMs plus standard treatment vs. standard treatment	N/A	N/D	N/D	N/A
	LDMs vs. Standard treatment	N/A	N/A	N/A	N/A
5. Lactone ring	LDMs vs. placebo	N/D	N/A	N/A	N/A
5.1 14-membered ring 5.2 15-membered ring	LDMs plus standard treatment vs. standard treatment	N/A	N/A	N/A	N/A
	LDMs vs. standard treatment	N/A	N/A	N/A	N/A
6. Duration	LDMs vs. placebo	N/A	N/A	N/A	N/A
6.1 > 12 weeks 6.2 12 weeks 6.3 < 12 weeks	LDMs plus standard treatment vs. standard treatment	Favor >12 weeks, SMD −1.68 (−2.40, −0.95)	Favor >12 weeks, SMD −1.65 (−2.37, −0.93)	Favor >12 weeks, SMD −3.79 (−4.85, −2.73)	N/D
	LDMs vs. standard treatment	N/A	N/A	N/A	N/A

CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; LDMs = low-dose macrolides; N/A = not applicable; N/D = no difference between subgroup; QOL = quality of life.

Table 2 Summary of findings from meta-analyses and subgroup analyses

Prognostic factor: CRS subtype

When subgroup analysis by CRS subtype was performed, the effects favored the LDM over placebo in the improvement in 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=0.009. The data is displayed in Figure2. Likewise, the effects favored the LDM 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=0.001. There was no difference between the two subgroups (p=0.64) in endoscopy score.

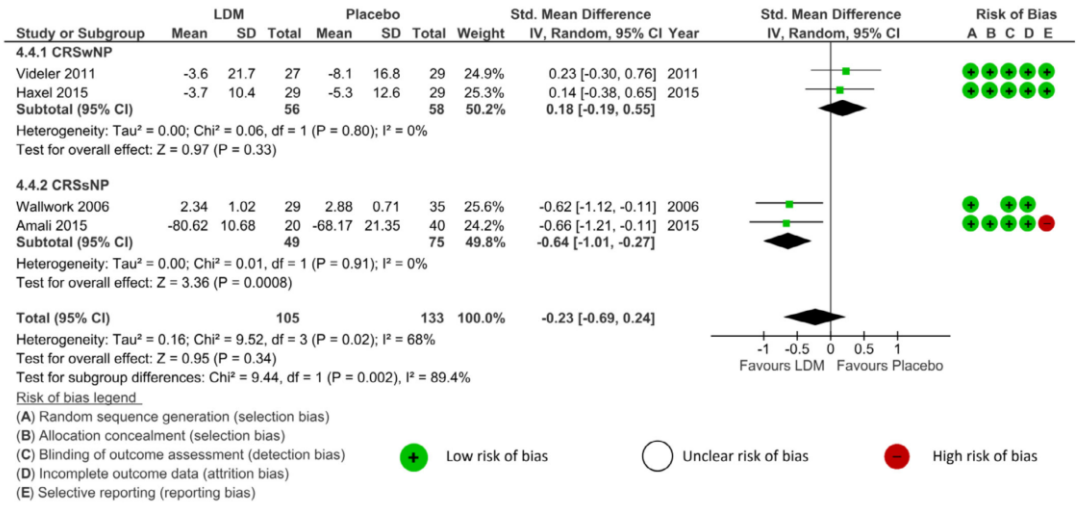

Fig. 2. Improvement in the SNOT at the end of treatment when low-dose macrolides therapy was compared with placebo and subgroup analysis by CRS subtype. CI = confidence interval; CRSsNP = chronic rhinosinusitis without polyps; CRSwNP = chronic rhinosinusitis with polyps; df = degrees of freedom; IV = inverse variance; LDM = low-dose macrolides; Random = random effects; SD = standard deviation; SNOT = Sino-Nasal Outcome Test; Std. mean difference = standardized mean difference. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Figure 2 Improvement in SNOT at the end of treatment when low-dose macrolides therapy was compared with placebo and subgroup analysis by CRS subtype

Prognostic factor: Serum IgE level

Two RCTs measured Serum IgE level at enrolment[5, 8]. 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, LDM brought greater symptom improvement when it was given to patients without ESS (MD -0.89, 95%CI -1.41 to -0.37) over the patients with ESS (MD 0.31, 95%CI -0.21 to 0.83). The subgroup difference was statistically significant, p=0.001. Improvements were similar between patients with and without ESS in SNOT improvement (the patients without ESS (SMD -0.20, 95%CI -1.03 to 0.63), and the patients with ESS (SMD -0.26, 95%CI -1.04 to 0.53), p=0.76) and endoscopy score (patients without ESS (MD -0.27, 95%CI -0.77 to 0.22), and patients with ESS (MD -0.45, 95%CI -0.97 to 0.08), p=0.64.

When LDM plus standard treatment was compared with standard treatment, meta-analyses gave results in contrast to the comparison of LDM versus placebo. LDM brought greater SNOT and

endoscopy score improvements when it was given to patients with ESS. The improvement in SNOT favored the patients with ESS (MD -1.68, 95% CI -2.40 to -0.95) but not the patients without ESS (SMD -0.01, 95% CI -0.63 to 0.61). The subgroup difference was statistically significant (p<0.001). The improvement in endoscopy score favored the patients with ESS (SMD -3.79, 95%CI -4.85 to -2.73), but not the patients without ESS (MD 0.02, 95%CI -0.46 to 0.51). The subgroup difference was statistically significant (p<0.001). 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=0.25).

Prognostic factor: Dose of macrolide

When subgroup analysis by dose of macrolides was performed, the effects favored the patients receiving half-dose macrolides (SMD -0.64, 95%CI -1.01 to -0.27), over the patients receiving less than half-dose macrolides (SMD 0.18, 95%CI -0.19 to 0.55), p=0.002. The data is displayed in Figure 3. Likewise, the effects in symptom score improvement favored the patients receiving half-dose macrolides (MD -0.89, 95%CI -1.41 to -0.37), over the patients receiving less than half-dose macrolides (MD 0.31, 95%CI -0.21 to 0.83), p=0.001. There was no difference between the two subgroups (p=0.64) in endoscopy score.

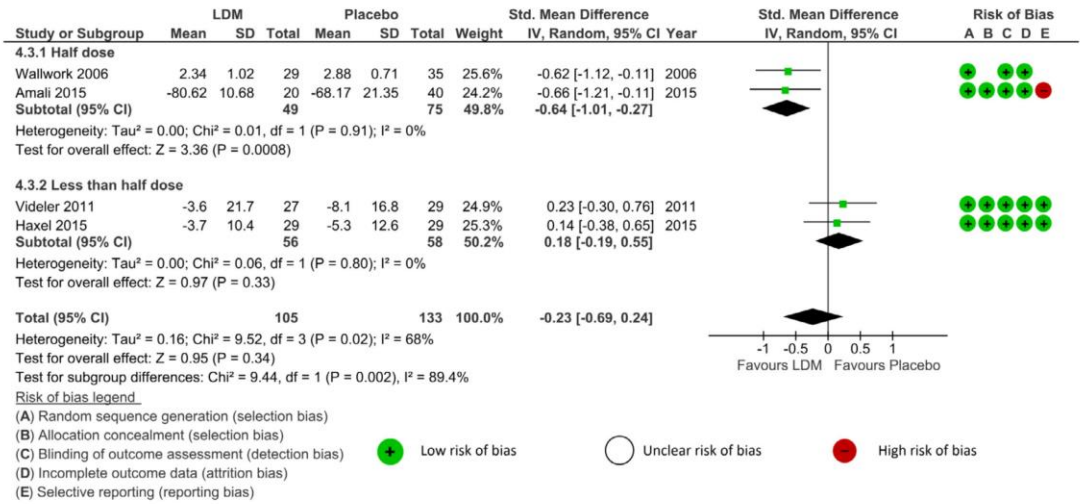

Fig. 3. Improvement in the SNOT at the end of treatment when low-dose macrolides therapy was compared with placebo and subgroup analysis by dosage. CI = confidence interval; df = degrees of freedom; IV = inverse variance; LDM = low-dose macrolides; Random = random effects; SD = standard deviation; SNOT = Sino-Nasal Outcome Test; Std. mean difference = standardized mean difference. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Figure 3 Improvement in SNOT at the end of treatment when low-dose macrolides therapy was compared with placebo and subgroup analysis by dosage

Prognostic factor: Membered lactone ring of LDM

When subgroup analysis by membered lactone ring of LDM was performed, the improvement in SNOT were similar between the patients receiving 14-membered lactone ring of LDM (SMD -0.24, 95%CI -0.98 to 0.50), and the patients receiving 15-membered lactone ring of LDM (SMD -0.21, 95%CI -1.09 to 0.66), p=0.96. The data is displayed in Figure 4.

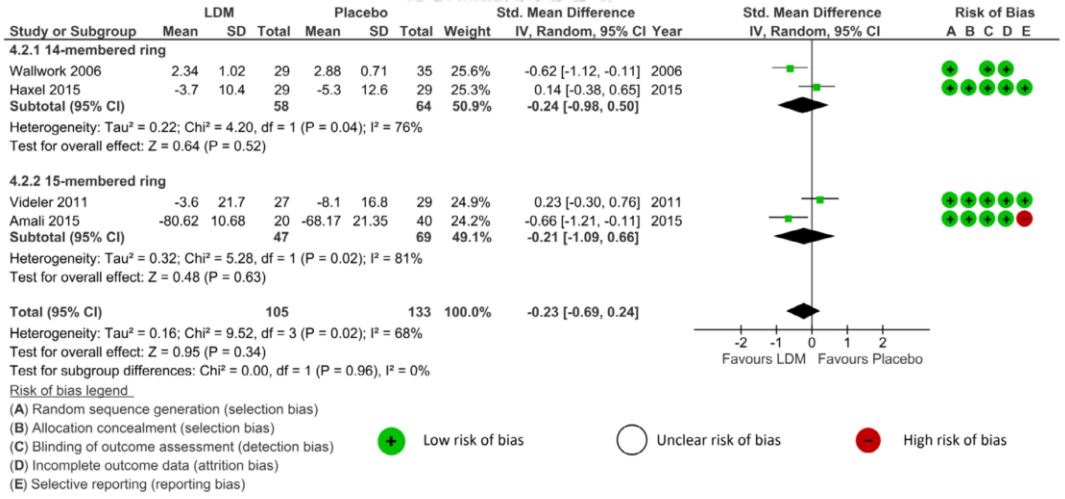

Fig. 4. Improvement in the SNOT at the end of treatment when LDM therapy was compared with placebo and subgroup analysis by membered ring of macrolides. CI = confidence interval; df = degrees of freedom; Fixed = fixed effects; IV = inverse variance; LDM = low-dose macrolides; SD = standard deviation; SNOT = Sino-Nasal Outcome Test; Std. mean difference = standardized mean difference. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Figure 4 Improvement in SNOT at the end of treatment when low-dose macrolides therapy was compared with placebo and subgroup analysis by membered-ring of macrolides

Prognostic factor: Duration of treatment

When subgroup analysis by duration of LDM treatment was performed, the effects in SNOT improvement favored the patients receiving 24-week LDM (SMD -1.68, 95%CI -2.40 to -0.95), over the patients receiving 12-week LDM (MD -0.28, 95%CI -0.77 to 0.21) and 8-week LDM (MD 0.36, 95%CI -0.33 to 1.04), p=0.002. Likewise, the effects favored the patients receiving 24-week LDM in symptom improvement (MD -1.65, 95%CI -2.37 to -0.93), over the patients receiving 12-week LDM (MD -0.10, 95%CI -0.59 to 0.38) and 8-week LDM (MD -0.29, 95%CI -0.73 to 0.15), p=0.001 and the effects favored the patients receiving 24-week LDM in endoscopy

score (MD -3.79, 95%CI -4.85 to -2.73), over the patients receiving 12-week LDM (MD 0.02, 95%CI -0.46 to 0.51), p<0.001. The effects at eight weeks by one RCT were not estimable. The improvement in CT score were similar between the patients receiving 12-week LDM (MD 0.08, 95%CI -0.40 to 0.56), and the patients receiving 8-week LDM (MD 0.28, 95%CI -0.40 to 0.96), p=0.64.

Adverse effects

There were 9 studies that reported gastrointestinal and cardiac adverse effects[5-8, 29-33]. LDM 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 is displayed in Table 3.

TABLE III.
Summary of Gastrointestinal and Cardiac Adverse Effects of LDMs Versus Other Treatments.

		Gastrointestinal Adverse Effects				Cardiac Adverse Effects			
		LDMs, No.		Other Treatments, No.		LDMs, No.		Other Treatments, No.	
First Author	Year	Event	Total	Event	Total	Event	Total	Event	Total
Wallwork	2006	1	29	1	35	0	29	0	35
Videler	2011	2	29	2	31	0	29	0	31
Jiang	2012	0	27	0	26	0	27	0	26
Peric	2014	2	40	0	40	0	40	0	40
Korkmaz	2014	1	22	0	22	0	22	0	22
Varvyanskaya	2014	1	44	0	22	0	44	0	22
Amali	2015	0	22	0	44	0	22	0	44
Haxel	2015	6	29	0	29	0	29	0	29
Deng	2018	1	38	0	36	0	38	0	36
		14	280	3	285	0	285	0	285

LDMs = low-dose macrolides.

Table 3 Summary of gastrointestinal and cardiac adverse effects of LDM versus other treatments

Durability of outcomes improvement

There were 4 studies that reported data after the end of the treatment at the timepoint of 24 weeks[5, 6, 8, 33]. The meta-analysis revealed no difference between the LDM and placebo in the improvement in (1) SNOT[5, 6] (SMD -0.28, 95%CI -0.64 to 0.09) (2) and endoscopy score[5, 8] (SMD -0.17, 95%CI -0.53 to 0.18) and no difference between the LDM plus standard treatment and standard treatment in the symptom score[33] (MD -0.06, 95%CI -0.49 to 0.16). At the timepoint of 48 weeks, Peric et al[33] reported no difference between the LDM 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[7, 33]. Both RCTs compared LDM plus standard treatment versus standard treatment. The results revealed two significant prognostic factors that the LDM was effective in SNOT improvement which were 1) CRSsNP and 2) half dose of LDM and three prognostic factors in symptom improvement which were 1) CRSsNP and 2) half dose of LDM and (3) LDM therapy without ESS.

Meta-regression analysis

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

2.4 Discussion

When compared to the controls, the overall effects of LDM for treating CRS did not favor the LDM in the improvement of any outcomes. To date, there have been four meta-analyses assessing the effects of LDM for treating CRS. Pynnonen et al.[35] pooled data from 2 RCTs and showed no benefit of the LDM over placebo at the end of treatment. Head et al.[8] extracted data from three RCTs. The meta-analysis included one RCT for each comparison and each outcome showed no benefit of the LDM therapy. Lasso et al.[36] pooled data from four RCTs and showed no difference between the effects of LDM and placebo. The recent meta-analysis by Shen et al.[37] included both randomized and non-randomized controlled trial. Forest plots from the RCTs did not show the benefit of LDM therapy.

Although the beneficial effects of LDM therapy were not evident by meta-analyses, substantial heterogeneity was shown. When six predictive factors were assessed by our study, subgroup

analyses revealed that the LDM was 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 anti-neutrophilic action and the suppression of the production of interleukin (IL)-8 and tumor necrosis factor-alpha (TNF-α) of the LDM therapy. The findings from subgroup analyses showed that the LDM therapy had beneficial effects in the improvement of 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/ non-eosinophilic inflammation. On the other hand, the CRSwNP associates with type 2 cytokines and high tissue eosinophilia[12]. Thus, its immunopathogenesis may not respond to the immunomodulation pathway of macrolides. The 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[9]. However, clinical studies showed controversies. Wallwork et al.[5] 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 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.[8] 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.[38] 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 non-responders (72 IU/mL). Recently, the local IgE production within the nose and paranasal sinuses in patients with CRS has been reported[17, 39]. Thus, the low serum IgE level may not be a good predictor to identify macrolide responders.

The included studies used various treatment regimens. Subgroup analyses in this study showed no difference between the 14-membered ring and the 15-membered ring LDM. The anti-inflammatory effects of LDM which interfere with the cytokine production and inflammatory cell metabolism were revealed in the 14- and 15-membered ring but not 16-membered ring macrolides[40, 41]. 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[42, 43]. These immunomodulatory effects of macrolides appear to be independent of the antimicrobial properties and the dosages of LDM are much lower than the minimum inhibitory concentration (MIC). However, there is no clear evidence that shows the optimal dose of the LDM. The dosages of LDM used by the included studies varied from half dose to very-low dose. When subgroup analyses were performed, the beneficial effects of LDM therapy over placebo in the improvement of SNOT and symptoms were shown in the subgroup using half-dose macrolides. This is in line with in vitro studies showing that the reduction of proinflammatory cytokine production is dose dependent. Kohyama et al.[41] and Wallwork et al.[44] assessed eosinophils and nasal mucosal tissue cultured, respectively and revealed the concentration-dependent reduction in IL-8. Duration of treatment is the other controversial issue. The included studies gave LDM therapy for various durations of 8, 12 and 24 weeks. The findings from subgroup analyses revealed that the 24 weeks duration of LDM 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 LDM therapy aims to cure the underlying etiologies. Thus, the duration of LDM therapy should not be limited to 12 weeks. Longer duration of LDM therapy may achieve better long-term disease control by the long-term anti-inflammatory and immunomodulatory effects.

Subgroup analyses by concurrent ESS in this study showed mixed results. Patients receiving LDM without ESS had greater improvement in symptoms than placebo. However, the patients receiving LDM with concurrent ESS had greater improvement in 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 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 LDM therapy without ESS was inferior to corticosteroids and ESS. Thus, the LDM therapy should not be the first line treatment for patients with CRS. Among the studies of LDM with concurrent ESS, Peric et al[33] did not find any benefit

of pre-operative LDM. The LDM 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 which predict the success of LDM therapy in patients with CRS. The findings suggested that LDM therapy provided clinical effectiveness to patients with CRSsNP. The LDM therapy should be an option for some groups of patients. When the LDM is considered, half-dose LDM for 24 weeks duration is recommended.

The limitation of this study is that the ten 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 enough power to see a statistically significant difference. The heterogeneity was substantial in some meta-analyses. Bias among the included studies was demonstrable.

2.5 Conclusion

Although overall beneficial effects were not demonstrated, LDM 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 LDM should be clinically effective in patients with CRSsNP. When the LDM is administered, half-dose of macrolides for 24 weeks duration is suggested. Favorable outcomes may be achieved in both patients receiving macrolides with and without ESS.

CHAPTER 3 LOW-DOSE MACROLIDES FOR TREATING PEDIATRIC RHINOSINUSITIS: A RETROSPECTIVE STUDY AND LITERATURE REVIEW

3.1 Introduction

Intranasal steroids, together with nasal saline irrigation have been the cornerstone of treatment of chronic rhinosinusitis (CRS)[45]. Refractory CRS is common in pediatric patients2 [46], and its management algorithm for this hard-to-treat condition is unclear. Empirical and culture-directed antibiotics are not recommended for treating pediatric CRS by European position paper on rhinosinusitis and nasal polyps 2020 (EPOS2020)1. Although intravenous antibiotics were shown beneficial, they were assessed by low-quality retrospective studies[46, 47], so they are not yet recommended. Surgical interventions for pediatric CRS, including adenoidectomy, sinus aspiration and endoscopic sinus surgery may be considered after medication failure[45]; nevertheless, there is no evidence supporting the use of this therapeutic options[48]. Besides, there is no consensus regarding the criteria and timing for surgery. Thus, the appropriate use of anti-inflammatory drugs, such as corticosteroids, doxycycline and macrolides may be able to reduce the need for surgery. As these agents have various mechanisms of action, understanding the inflammatory pattern of pediatric CRS is essential for controlling this refractory disease.

Pathogenesis, endotyping and the pattern of the inflammation of pediatric is different from adult CRS. Although, in general, the adult CRS represents multiple overlapping entities, most adult refractory CRS are chronic rhinosinusitis with nasal polyps (CRSwNP) which associates with T helper (Th) 2-skewed eosinophilic inflammation with elevated levels of interleukin (IL)-5, eotaxins and eosinophilic cationic protein[1-3]. In contrast, most pediatric refractory CRS are CRS without nasal polyps (CRSsNP) and associates with Th1/Th17-skewed neutrophilic inflammation with elevated levels of interferon-γ, transforming growth factor-β, IL-17, Myeloperoxidase, IL-6, IL-8, and IL-1β[49]. When choosing anti-inflammatory agents to the individual patient, patients with CRSwNP are acknowledged corticosteroid responsive[50] and should respond to the anti-MMP9 property of doxycycline[4] while patients with CRSsNP should respond to the anti-neutrophilic property of long-term low-dose macrolide (LDM) therapy. Based on this rationale, long-term LDM should provide benefit to pediatric refractory CRS as it modulates neutrophilic

action by suppressing lipopolysaccharide-induced neutrophil migration. The production of pro-inflammatory cytokines, such as IL-8 and tumor necrosis factor-alpha (TNF-α) is suppressed. In addition, the LDM modulates the synthesis and secretion of mucus and alters the mucus rheological properties resulting in an effective mucus clearance[16].

Currently, the recommendation of LDM therapy regarding patient selection is controversial. While two international guidelines suggest LDM therapy for both CRSsNP and CRSwNP[11, 45], another guideline does not suggest LDMs at all[51]. A recent systematic review and meta-analysis revealed that LDM therapy is effective only in CRSsNP[52]. However, these recommendations are based on clinical studies on adult rhinosinusitis. To date, there has never been any study assessing the clinical effectiveness of LDMs for treating pediatric CRS; therefore, it has not been mentioned in any international guidelines. This preliminary study aimed to investigate the effects of LDMs on pediatric CRS patients who did not respond to the standard treatment. In addition, we reviewed the literature regarding the pathophysiology of pediatric CRS and the mechanisms of action of macrolides in treating CRS in the pediatric population. Any clinical trial studying the effects of macrolides in pediatric CRS was included in this review.

3.2 Methods

A retrospective study was conducted by a medical chart review. This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB 085/62). Pediatric patients with uncontrolled CRS who received LDM after standard medical treatment failure between 2013-2019 were identified. The uncontrolled CRS was defined as (1) had at least 3 of these symptoms during the past month: nasal blockage, rhinorrhea or postnasal drip, facial pain or headache, loss of smell, and sleeping disturbance or fatigue, (2) physician assessment showed a diseased mucosa (nasal polyps, mucopurulent secretions, or inflamed mucosa), and (3) systemic medications were required during the past month[45]. Standard medical treatment[45] included empirical or culture-directed oral antibiotics, nasal saline treatment, and intranasal steroids. Patient characteristics (gender, age, nasal polyps, asthma, rhinitis, aspirin hypersensitivity, passive smoker, gastroesophageal reflux, previous sinus surgery, previous medications) and duration of symptoms were collected.

Inclusion criteria

The inclusion criteria were (1) age <15 years old, (2) diagnosed with CRS according to the diagnostic criteria described in the EPOS2012[9], (3) the duration of rhinosinusitis of more than 3 months, (4) received any macrolide agents, any doses and regimens for ≥6 weeks, (5) had uncontrolled CRS, (6) received but not responded to an appropriate standard medical treatment, and (7) any co-interventions were allowed.

Exclusion criteria

The exclusion criteria were (1) previous sinus surgery, (2) neoplasms of nasal and/or sinus mucosa, (3) cystic fibrosis, (4) systemic vasculitis and granulomatous diseases, (5) gross immunodeficiency (congenital or acquired), (6) congenital mucociliary problems (e.g. primary ciliary dyskinesia), and (7) non-invasive fungal balls or invasive fungal disease.

Outcomes

The outcomes were (1) total nasal symptoms (TNS) by the visual analogue scale, (2) the presence of individual symptoms: nasal obstruction, rhinorrhea, hyposmia, facial pain and cough, (3) the presence of nasal discharge by physician-assessment: no discharge, thin watery, thick mucoid or purulent and (4) adverse events.

Statistical analysis

As this is the first study assessing the effects of low-dose macrolides in treating pediatric rhinosinusitis, data were not available for sample size calculation. The data from this preliminary study should be used for sample size estimation for further studies. Descriptive data were presented as a percentage or mean ± standard deviation (SD) where appropriate. The outcomes were compared between before and after the LDM therapy. A paired T-test was used for paired continuous variables, and McNemar's test was used for paired nominal variables. Statistical significance was determined when a p-value was less than 0.05. Statistical analyses were performed using SPSS v 22.0 (Statistical Package for the Social Sciences, Chicago, IL).

3.3 Results

Six patients (67% male, mean age 7±3.4 years) were identified. All patients had rhinitis together with rhinosinusitis symptoms such as sneezing, itching and watery, itchy eyes. Two patients were diagnosed as allergic rhinitis, confirmed by skin prick test, and one of them received subcutaneous immunotherapy for house dust mite and cockroach allergy. No patient had asthma, history of gastroesophageal reflux, aspirin hypersensitivity or previous endoscopic sinus surgery. One patient was a passive smoker. The mean duration of symptoms was 7.8±4.6 months. The demographic data are displayed in Table 4.

ID	Age (years)	Sex	Duration of symptom (months)	CRS subtype	Rhinitis symptom	Asthma	Aspirin hypersensitivity	Passive smoker	Reflux	Previous surgery
1	8	F	3	CRSsNP	Yes	No	No	No	No	No
2	10	M	3	CRSsNP	Yes	No	No	Yes	No	No
3	7	M	5	CRSsNP	Yes	No	No	No	No	No
4	3	M	12	CRSsNP	Yes	No	No	No	No	No
5	3	F	12	CRSsNP	Yes	No	No	No	No	No
6	11	M	12	CRSsNP	Yes	No	No	No	No	No

ID: identification number; CRS: chronic rhinosinusitis; CRSsNP: chronic rhinosinusitis without nasal polyp; F: female, M: male.

Table 4 Demographic data of the patient population

Two patients received roxithromycin, and four patients received clarithromycin. The LDM dosages that all patients received were half of the standard anti-bacterial dose. The mean duration of LDM therapy was 14.2±5.4 weeks. All patients received intranasal steroids and nasal saline irrigation as co-interventions. The co-interventions were the standard treatment previously prescribed which the patients chose to continue despite the failure of the treatment. Data are displayed in Table 5.

ID	LDMs	Duration of LDMs (weeks)	Previous medication				Co-intervention			
			Non-LDM antibiotics	Steroids	Nasal irrigation	Other medications	Non-LDM antibiotics	steroids	nasal irrigation	other medications
1	Roxithromycin 150 mg 1 tab od	8	Cefditoren (100 mg) 1 tab oral bid 3 weeks	Fluticasone furoate spray 1 puff bid	Nasal saline irrigation bid	0.03% Ipratropium, bromide spray 2 puff qid	None	Fluticasone furoate spray 1 puff bid	Nasal saline irrigation bid	0.03% Ipratropium, bromide spray 2 puff qid
2	Clarithromycin 500 mg 1 tab od	9	Cefditoren (100 mg) 1 tab oral bid 3 weeks	Mometasone furoate spray 1 puff bid	Nasal saline irrigation	0.05% Oxymetazoline nasal spray 2 puff bid	None	Mometasone furoate spray 1 puff bid	Nasal saline irrigation bid	0.05% Oxymetazoline nasal spray 2 puff bid
3	Roxithromycin 150 mg 1 tab od	22	Amoxicillin/clavulanic acid (1 g) 1 tab oral bid 2 weeks, levofloxacin (500 mg) 1 tab oral od 1 week, moxifloxacin (400 mg) 1 tab oral od 1 week	Mometasone furoate spray 1 puff bid	Nasal saline irrigation bid	Montelukast (5) 1 tab oral hs, desloratadine (5) 1 tab oral hs	None	Mometasone furoate spray 1 puff bid	Nasal saline irrigation bid	None
4	Clarithromycin 3.25 mg/kg/day	17	Amoxicillin/clavulanic acid (1 g) 1 tab, oral bid 2 weeks, levofloxacin (500 mg) 1 tab oral od 1 week, moxifloxacin (400 mg) 1 tab oral od 1 week	Fluticasone furoate spray 1 puff bid	Nasal saline irrigation bid	0.05% Oxymetazoline nasal spray 2 puff bid, montelukast (5) 1 tab, oral hs, desloratadine (5) 1 tab oral hs	None	Fluticasone furoate spray 1 puff bid	Nasal saline irrigation	Montelukast (5) 1 tab oral hs
5	Clarithromycin 3.25 mg/kg/day	17	Amoxicillin/clavulanic acid (1 g) 1 tab oral bid 2 weeks, levofloxacin (500 mg) 1 tab oral od 1 week, moxifloxacin (400 mg) 1 tab oral od 1 week, 0.05%	Fluticasone furoate spray 1 puff bid	Nasal saline irrigation bid	Oxymetazoline nasal spray 2 puff bid, montelukast (5) 1 tab oral hs, desloratadine (5) 1 tab oral hs	None	Fluticasone furoate spray 1 puff bid	Nasal saline irrigation bid	Montelukast (5) 1 tab oral hs
6	Clarithromycin 250 mg od	12	Amoxicillin/clavulanic acid (1 g) 1 tab, oral bid 3 weeks	Budesonide (1 mg) in normal saline 250 mL nasal irrigation od		None	None	Budesonide(1 mg) in normal saline 250 mL nasal irrigation od		None

ID: identification number; LDMs: low-dose macrolides; tab: tablet; od: once a day; bid: two times a day; qid: four times a day; hs: before sleep.

Table 5 Summary of medical therapy

The TNS were significantly improved after the addition of LDM therapy (mean difference ± SD 5.83 ± 1.33, 95% CI 4.44 to 7.23, p< 0.001). LDM decreased the numbers of patients who had symptoms and signs including, nasal obstruction (from 100% to 67%), rhinorrhea (from 83% to 50%), hyposmia (from 50% to 0%), cough (from 100% to 33%), and thick mucoid discharge (by physician assessment) (from 33% to 0%). No patient had facial pain and purulent discharge (by physician assessment) neither pre-treatment nor at the end of treatment. One patient reported mild, tolerable nausea. Data are displayed in Table 6.

	Pre-LDMs	Post-LDMs	p value
TNS, mean ± SD	8.67 ± 1.03	2.83 ± 1.33	<0.01*
Nasal obstruction, n (%)	6/6 (100%)	4/6 (67%)	N/A
Rhinorrhea/PND, n (%)	5/6 (83%)	3/6 (50%)	1.00
Facial pain, n (%)	0/6 (0%)	0/6 (0%)	N/A
Loss of smell, n (%)	3/6 (50%)	0/6 (%)	N/A
Cough, n (%)	6/6 (100%)	2/6 (33%)	N/A
Physician assessment nasal D/C			N/A
No D/C	1/6 (17%)	5/6 (83%)	
Thin watery D/C	1/6 (17%)	1/6 (17%)	
Thick mucoid D/C	2/6 (33%)	0/6 (0%)	
Purulent D/C	0/6	0/6 (0%)	

TNS: total nasal symptom, LDMs = low-dose macrolides, D/C = discharge, PND = postnasal drip; N/A: not applicable (McNemar's test cannot be done when one of the cell frequencies is 0.)
*p < 0.05.

Table 6 Clinical effectiveness of LDMs therapy

3.4 Discussion

Literature review

Inflammatory pattern of pediatric CRS

Pediatric refractory CRS associate with Th1/Th17-skewed neutrophilic inflammation. The levels of the cytokine tumor necrosis factor-alpha, the antimicrobial peptide human beta-defensin 2 and neutrophil-released calprotectin in nasal lavages of pediatric patients with CRS were found higher than healthy controls[53]. Chan et al.[49] assessed histopathology of the maxillary sinus mucosa of pediatric patients with CRS, compared to adult CRS. The density of tissue eosinophils was significantly less in the pediatric group. While adult has thicker epithelium and basement membrane thickening, pediatric CRS patients had a higher density of tissue lymphocytes. Also, when immunohistopathology was assessed[54], the pediatric group showed more CD8+, MPO+, and CD68+ cells in their epithelium and more CD20+, kappa+ and lambda+, MPO+, and CD68+ cells in their submucosa which represented higher numbers of neutrophils, macrophages, B lymphocytes, and plasma cells. Wu et al.[55, 56] performed immunohistochemical analysis to assess gene expression of inflammatory mediators in the sinus tissue by using microarray analyses. Expression of inflammatory genes was found increased for both innate immune system including serum amyloid A2 (SAA2), serpin peptidase inhibitor member 4 (serpin B4), and beta-defensin 1 (DEFB1) and adaptive immune system including the cytokines CXCL5 (neutrophil chemoattractant), and CXCL13 (B lymphocyte chemoattractant) in pediatric CRS patients. Coimmunofluorescence staining of inflammatory cells revealed that these gene products were expressed at the protein level and exhibited cell-specific localization. CXCL13 was expressed in macrophages, T and B cells, and CXCL5 was detected in T cells. Ciliated and basal cells in the pseudostratified epithelium stained positively for all five mediators. Increased messenger RNA expression in submucosal glands was revealed. Likewise, Saieg, et al.[57] demonstrated an increase of MUC5B, the predominant glandular mucin in the secretory mucin of pediatric patients with CRS.Hypertrophic adenoid in children causes poor drainage with bottleneck obstruction at the posterior choana. Additionally, hypertrophic adenoid is a reservoir of bacteria. Shin et al.[58] assessed a correlation between adenoid tissue bacterial culture, rhinosinusitis severity and adenoid

size. Bacterial isolation rate increased significantly according to rhinosinusitis severity, especially Haemophilus influenzae and Streptococcus pneumonia with regardless of adenoid size. Zuliani et al.[59] found dense bacteria biofilm covering the mucosal surface of adenoid tissue removed from pediatric patients with CRS, but not from patients with obstructive sleep apnea. A reservoir of bacteria and biofilms results in antibiotic-resistant chronic bacterial infection[59]. When immunoassays were performed on adenoid tissues of pediatric patients with CRS to assess the expressions of inflammatory cell activation markers and tissue remodeling, Shin, et al.[60] found higher levels of the T cell activation marker soluble interleukin-2 receptor (sIL-2R), and higher levels of cytokines associated with tissue remodelling including transforming growth factor β-1 (TGFβ-1), matrix metalloproteinases (MMP) 2 and 9, and tissue inhibitor of metalloproteinase (TIMP-1). The level of the eosinophil activation marker was not different between pediatric patients with and without CRS. Anfuso, et al.[61] assessed the expression of a vast array of inflammatory cytokines and chemokines in the sinus and adenoid tissues of pediatric patients with CRS with and without asthma. They showed that the inflammatory response in the sinus and adenoid tissues of pediatric patients with CRS and asthma was similar.

Effects of LDM therapy for pediatric CRS

All pediatric patients in this study received LDM therapy with intranasal steroid spray co-intervention. The beneficial effects shown could be either the sole effects of LDM or the combined effects of the LDM and intranasal steroids. The mechanisms of the anti-inflammatory effects of LDM are different from the anti-inflammatory effects of steroids. Intranasal steroid binds to a specific cytoplasmic glucocorticoid receptor then activates anti-inflammatory gene transcription and represses pro-inflammatory gene transcription. As a result, the lymphocyte activation and cytokine production are inhibited, which decrease inflammatory cells migration to the nasal mucosa[62]. The mechanism of antineutrophilic action of LDMs is associated with the suppression of the production of IL-8 and TNF-α[49, 63-66].

Furthermore, the LDMs have been shown to decrease mucus formation, secretion, and viscosity[49, 67, 68]. The effects on mucus reduction are due to anti-inflammatory activities rather than a direct effect on mucus-producing cells. Macrolides inhibited the quorum-sensing circuitry and block

biofilm formation of the bacteria and were shown to have beneficial effects in the management of cystic fibrosis and diffuse panbronchiolitis[69, 70]. Based on these rationales, LDM therapy with antineutrophilic property should be effective in pediatric patients with refractory CRS. The addition of LDM could provide synergistic effects to intranasal steroids. The combination effects include (1) the suppression of cytokine production[71] the reduction of inflammatory cell migration, (3) the decrease in mucus production and viscosity, (4) the improvement of mucociliary function, (5) the mechanical wash of mucopurulent discharge and (6) the promotion of ventilation and drainage of the paranasal sinuses. These combined effects could offer more benefit than monotherapy.

To the best of our knowledge, this is the first study assessing the effectiveness of LDM therapy in pediatric refractory CRS. The effects of LDM therapy shown by this study was not only statistically significant but also clinically meaningful. The average score of symptom improvements was around 6 out of the maximum score of 10. Individual symptoms were absent in most patients. The physician-assessment nasal discharge, including thick mucoid and purulent discharge, were no longer present in all patients. All patients in this study had CRSsNP subtype. Compared to adult CRS, neutrophilic inflammation was more prevalent in pediatric CRS[49, 72, 73] and among pediatric patients with CRS, the inflammatory patterns were more neutrophilic than eosinophilic inflammation[49]. Thus, the age and CRS subtype of the patients in this study suggested the neutrophilic/non-eosinophilic inflammatory pattern, driven by type 1/type 17 cytokines.

In line with our study, a recent meta-analysis showed that patients with CRSwNP did not respond to the combination of LDM therapy and steroids, compared to steroids alone[52]. In addition, it suggested that LDM therapy was effective for patients with CRSsNP, regardless of the difference between the 14 and 15 membered ketone rings of macrolides. The LDM therapy should be given at half of the full dosage of anti-bacteria for a duration of longer than 3 months[52]. There were no serious adverse effects reported in this study; however, one patient reported mild, tolerable nausea. This effect was in line with the recent meta-analysis that reported LDMs produced more significant gastrointestinal adverse effects (5%) when compared to other treatments (1.05%) (risk ratio: 3.52; 95% CI: 1.29 to 9.60) and there was no cardiac adverse effect reported in any

patients[52]. Based on the findings of this study, the authors suggest that LDM therapy could be second-line medical treatment for pediatric CRS. Clinicians should consider LDM therapy when the pediatric CRS is refractory and not respond to empirical oral antibiotics, intranasal steroids and nasal saline irrigation. This option should be considered before adenoidectomy, sinus aspiration and endoscopic sinus surgery. The intranasal steroids and nasal saline irrigation may be continued during the LDM therapy. Biologic treatment in pediatric CRS was not addressed due to there was no study in pediatric from the recent Cochrane review[74]. Moreover, the dominant inflammatory pattern of pediatric CRS was not type 2 inflammation. Consequently, the biologic treatment, which was suitable for type 2 inflammation, did not have a role in pediatric CRS nowadays[74].

The limitations of this study included the retrospective nature of the study design. The sample size of this study was too small to get conclusions as it is a preliminary report about the beneficial effects of LDM therapy in pediatric refractory CRS. The co-interventions and confounder factors could not be controlled due to the nature of the study. Although this study aimed to assess the sole effects of LDM therapy, all included patients continued using intranasal steroid spray and nasal saline irrigation. This could be because the LDM therapy has not been studied in pediatric patients and not recommended by any guidelines. Other confounders such as decongestants, ipratropium, bromide spray and leukotriene receptor antagonists may provide additional effects to the treatment. Biomarkers of the immunopathogenesis were not assessed. A well-conducted randomized controlled trial of LDM therapy versus placebo with a sample size calculation using the data from this preliminary study are required to demonstrate evidence of the additional effects of low-dose macrolide in pediatric patients. Co-interventions should not be allowed in order to determine the effects of individual LDM therapy.

3.5 Conclusion

The preliminary findings of this study showed some beneficial effects of the LDM therapy added to intranasal steroids and nasal saline irrigation, in pediatric CRS that failed standard treatments. The LDM therapy showed improvements in: total nasal symptom score, nasal obstruction, rhinorrhea, hyposmia, cough and physician-assessment thick mucoid discharge. LDM therapy should be considered in pediatric refractory CRS patients in clinical practice.

CHAPTER 4 PREDICTIVE FACTORS FOR IDENTIFYING MACROLIDE RESPONDER IN TREATING CHRONIC RHINOSINUSITIS

4.1 Introduction

Chronic rhinosinusitis (CRS) represents multiple overlapping entities with various inflammatory patterns. The classification of CRS according to its phenotype into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) may not accurately represent the underlying inflammation. Diversity in CRS pathogenesis associates with a broad spectrum of immunologic profiles and expressions of various Th cell types. The recent European position paper on rhinosinusitis and nasal polyps 2020 (EPOS 2020) used endotype dominance for CRS classification[45]. Type 2 CRS is acknowledged Th2-skewed eosinophilic inflammation with elevated levels of interleukin-5 (IL-5), immunoglobulin E (IgE), eotaxins, and eosinophilic cationic protein (ECP). The biomarkers of this CRS subtypes include IL-4, IL-5, IL-13, IL-25, IL-33, TSLP, and IgE. Whereas non-type 2 is acknowledged Th1/Th17-skewed neutrophilic inflammation with elevated levels of interferon-γ (IFNγ), transforming growth factor-β (TGFβ), IL-17, Myeloperoxidase (MPO), IL-6, IL-8, IL-1β[2, 3, 45]. Its biomarkers include IFN-γ, IL-17, IL-22[2, 3, 45]. In comprehensive medical treatment for CRS with various types of inflammation, anti-inflammatory drugs become the primary medical therapy.

Macrolides are acknowledged as anti-inflammatory agents with antineutrophilic activity[16]. Patient selection for low-dose macrolides (LDM) therapy was a controversial issue among various international guidelines. International Consensus Statement on Allergy and Rhinology (ICAR) recommends LDM therapy as an option in a patient with both CRSsNp and CRSwNP[11]. In contrast, a meta-analysis by our group assessed prognostic factors that predicted favorable outcomes of LDM in treating CRS and found benefits in patients with CRSsNP as opposed to CRSwNP[52]. EPOS 2020 recommends long term LDM as an optional treatment in a patient with non-type 2 primary diffuse CRS[45]. By rationale, LDM have antineutrophilic activity so they should not work for eosinophilic inflammation in type 2 CRS. However, simultaneous expression of multiple Th cell types has been shown in some patient clusters. Clinical predictors therefore are required to appropriately select the favorable patients for LDM therapy.

Low level of serum IgE has been recommended as a biomarker for defining LDM responders[9]. Although it was evident by one randomized controlled trial[5], the following studies reported different results[8, 38]. In fact, level of serum IgE may not be an appropriate biomarker due to a growing body of evidence showing local IgE production in rhinosinusitis[1]. Specific local IgE can be present in patients having low serum IgE with negative systemic allergy testing. There was an association between eosinophilic inflammation in nasal polyps and the increased levels of total local IgE, and specific local IgE. In addition, evidence of nasal secretion IL-5 in type 2 CRS was revealed[1].

When IgE and IL-5 were produced locally in patients with type 2 CRS[45]. The low levels of local IgE and local IL-5 should be more suitable predictive markers than the low serum IgE to identify LDM responders.This study aims to assess individual predictive factor and propose suitable multiple predictive factors for identifying a macrolide responder in treating CRS. We hypothesized that the low level of nasal secretion IgE and IL-5 should be ones of the suitable criterion.

4.2 Methods

Patient population

This study is prospective cohort design. Patients presented with CRS at the King Chulalongkorn Memorial Hospital from August 2018 to May 2020 were recruited. Inclusion criteria were: (1) patients with CRS following the diagnostic criteria recommended by EPOS2012[9], and (2) age between 18-70 years. Exclusion criteria were: (1) macrolide allergy, (2) Pregnancy, (3) Chronic liver and heart disease, (4) Use of systemic steroid for the past 4 weeks and/or topical steroid for the past 2 weeks, (5) Previous sinus surgery, (6) Neoplasm of nasal and sinus mucosa, (7) cystic fibrosis, systemic vasculitis and granulomatous diseases, (8) gross immunodeficiency (congenital or acquired), (9) congenital mucociliary problems (e.g., primary ciliary dyskinesia (PCD)), (10) non-invasive fungal balls and invasive fungal disease, (11) cocaine abuse[9]. They were provided with all details and ample time to ask questions that included potential risks and benefits from the study. All volunteers signed informed consent. The study was approved by the Institutional

Review Board of the Faculty of Medicine, Chulalongkorn University (number 195/60). This research is granted by "The 90th Anniversary of Chulalongkorn University Scholarship".

Data collection

Clinical data collection includes nasal obstruction, nasal discharge (anterior/posterior nasal drip), facial pain/ pressure, loss of smell, age, sex, history of asthma and aspirin hypersensitivity. Asthma was defined as clinically using an inhaled β-agonist or corticosteroid. Aspirin hypersensitivity was defined on history of an acute exacerbation of bronchoconstriction and other symptoms of asthma after ingesting aspirin or other NSAID. The CT scan of the paranasal sinus was done to confirm the diagnosis of CRS. Lund-Mackay CT score[75], the total nasal symptoms visual analogue scale (VAS)[45] and Thai version of sino-nasal outcome test 22 (SNOT-22)[76] were assessed for CRS disease severity. The nasal polyp was evaluated by nasal endoscopy. Serology was assessed for serum total IgE, serum eosinophil, and serum neutrophil. Allergy status was assessed with the skin prick test using fifteen common local aeroallergens. Nasal secretions were obtained by inserting a dehydrated sponge composed of hydroxylated polyvinyl acetate (Merocel, Medtronic Inc., Minneapolis, Minnesota, USA) in each middle meatus for 5 minutes. The secretion was extracted from the sponge by adding 2 mL of 0.9% sodium chloride solution. All sponges were stored at 4° C for 2 hours and then transferred to a 5-mL syringe. The bulk of the nasal secretion was forced out of the sponges using the syringe's piston and centrifuged at 1,500 g for 15 minutes at 4° C. The supernatants were separated and stored in aliquots at -20 ° C until analysis[77]. The level of total IgE was assessed using fluoroenzyme immunoassay (ImmunoCAP; Phadia, Sweden). The concentrations of IL-5 were determined by Enzyme-linked immunosorbent assay (ELISA) (Human IL-5 ELISA Kit, Abcam, UK).

LDM therapy

Patients received 150 mg of roxithromycin once daily for 12 weeks. They were asked to rinse their noses with nasal saline irrigation twice a day. There were three follow-up visits at 4 weeks, 8 weeks, and 12 weeks. The total nasal symptoms VAS was evaluated at every visit. If the patients had total nasal symptoms VAS greater than 7^9 at any visit, they were defined as macrolides non-

responders. Roxithromycin was discontinued and rescue medications were given. Intranasal corticosteroids and/or oral corticosteroids were chosen according to the disease severity. Oral antibiotics were given when acute bacterial exacerbation was suspected. Concomitant drug use in the past month and the number of missing tablets were recorded.

Predictors for macrolide responders

Nine potential predictors for macrolide responders assessed in this study were (1) nasal secretion total IgE level, (2) nasal secretion total IL-5 level, (3) serum total IgE level, (4) serum eosinophil level, (5) serum neutrophil level, (6) presence of nasal polyp, (7) history of asthma, (8) positive allergy test for allergic rhinitis (9) history of ASA hypersensitivity. At the endpoint of 12-week follow-up, the patients were defined as either macrolide responders or non-responders. The criteria of macrolide responder were (1) improvement in SNOT22 of greater than one minimal clinically important difference (MCID; 9 points)[78] at 12 weeks AND; (2) total nasal symptoms VAS ≤ 5[45] at 12 weeks AND; never requiring rescue medicine at any time point for the whole three months.

Statistical Analysis

Statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX, USA). Each of the predictors was dichotomized at a cut-point to maximize the sensitivity and specificity[79]. The performance characteristics, including sensitivity, specificity, accuracy, and likelihood ratios, were derived at this cut-point. In addition, we calculated the area under the ROC curve, which is a measure of model discrimination. Univariable logistic regression was used to calculate diagnostic odds ratios for each biomarker, and multivariable logistic regression was then used to select a model of multiple potential factors for identifying macrolide responders in treating CRS. We used backwards stepwise selection, first entering all terms with $P<0.1$ in univariate models, and retaining terms, then sequentially dropping the term with the highest (least-significant) P-value until all remaining terms were significant at $P<0.1$. Scatterplots of serum versus local IgE were used to assess whether the relationship between these parameters was linear. Due to clustering at low values and a number of outliers, Spearman's correlation was used to assess the strength of the

monotonic relationship between serum IgE and local IgE. The mean and median local IgE level between the skin prick test positive and negative groups was also compared. Statistical significance was taken at P-values ≤ 0.05.

4.3 Results

There were 105 patients with CRS who enrolled in the study; however, 3 patients failed to complete the study due to general medical conditions (1 pregnancy, 1 hematologic disease, 1 cardiac disease), and 2 patients were lost to follow up. A total of 100 patients (mean–±SD age 47.35 ± 14.13 years, 45% male) with CRS were included. 22% had asthma, 38% were atopic, and 6% had aspirin sensitivity. 37 % had nasal polyps observed on nasal endoscopic examination, 91% complained of nasal obstruction, 94% had nasal discharge (anterior/posterior nasal drip), and 39 % had facial pain, and 63% had a loss of smell. Baseline VAS of 100 patients was (mean ± SD) 4.97 ± 2.9, SNOT-22 score was 43.99 ± 18.84, and Lund Mackay CT score was 12.38 ± 4.3.

Twenty-six macrolides non-responders had VAS > 7 at the 4th weeks. Intranasal corticosteroids were given in all cases, 13 patients received oral corticosteroids, and 1 patient received oral antibiotics. At eight weeks, 74 patients came to a second follow-up. Six macrolides non-responders had VAS > 7. Intranasal corticosteroids were given in all cases, and one patient received oral corticosteroids. At the end of the treatment, 29 patients met the criteria of macrolide responders (Figure 5). Each of the predictors was dichotomized at a cut-point to maximize the sensitivity and specificity based on ROC curve analysis. The serum total IgE, local total IgE, local IL-5, serum eosinophils, and serum neutrophils were 60 lg/L, 4.76 kU/l, and 0.27 pg/ml, 3.7%, and 58%, respectively. The area under the ROC curve (AROC), sensitivity, specificity positive likelihood ratio (LR+), and negative likelihood ratio of all predictors were shown in Table 7.

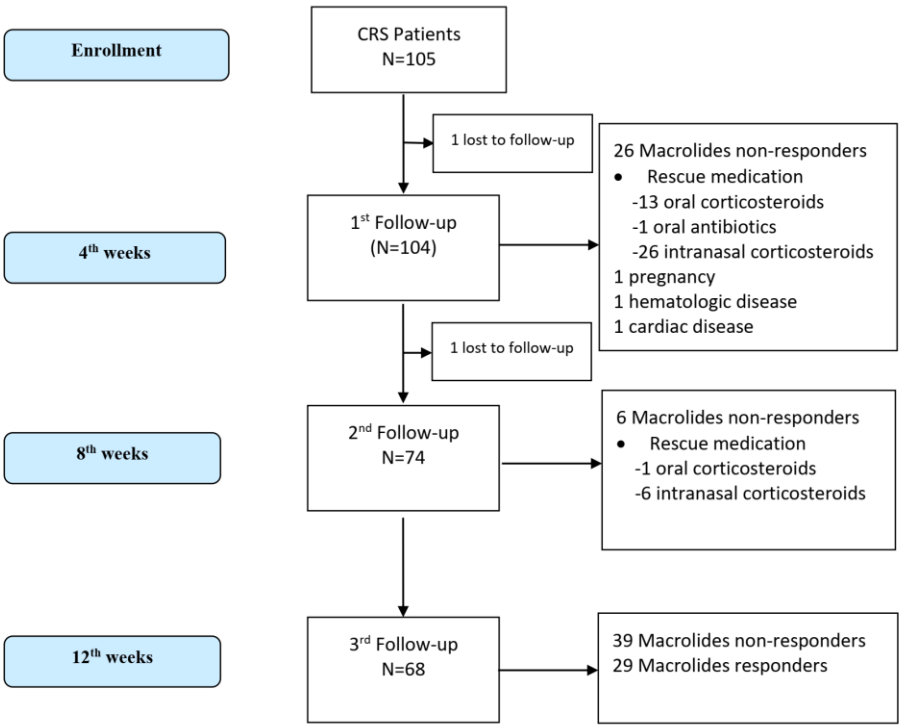

Figure 5 Flow diagram of the study

Variable (dichotomized)	AROC (95%CI)	Sensitivity	Specificity	LR+	LR-
Serum IgE <60	0.60 (0.49 - 0.71)	55.17	64.79	1.57	0.69
Local IgE <4.76	0.63 (0.53 - 0.72)	75.86	49.30	1.50	0.49
Local IL5 <0.27	0.59 (0.49 - 0.70)	65.52	57.00	1.40	0.64
Serum eosinophils < 3.7%	0.61 (0.5 - 0.72)	58.62	63.38	1.60	0.65
Serum neurotrophils <58%	0.52 (0.41 – 0.62)	55.17	47.89	1.06	0.94
Presence of polyps	0.62 (0.51 – 0.72)	44.83	78.87	2.12	0.70
Asthma	0.58 (0.47 – 0.69)	48.28	67.61	1.49	0.77

ASA sensitivity	0.44 (0.36 – 0.52)	13.79	74.65	0.54	1.15
SPT positive	0.53 (0.47 – 0.59)	10.34	95.77	2.45	0.94

Table 7 The area under the ROC curve (AROC), sensitivity, specificity positive likelihood ratio (LR+), and negative likelihood ratio (LR-) of all predictors

Univariable logistic regression was conducted with the dichotomized biomarkers and other potential categorical predictors of response. Only local total IgE < 4.76 kU/l (OR: 3.06, 95%CI: 1.16 - 8.06, P= 0.02); and serum eosinophils < 3.7% (OR:2.45, 95%CI 1.01 – 5.93, P=0.046) showed a statistically significant association with macrolide response (Figure 6). Moreover, in a multivariate backward stepwise regression model, local total IgE was the only variable that maintained an independent association with macrolide response(OR: 3.06, 95%CI: 1.16 - 8.06, P= 0.02), with an ability to discriminate between responders and non-responders of 63% (area under the ROC curve = 0.63, 95%CI: 0.53 – 0.72) (Table 8).

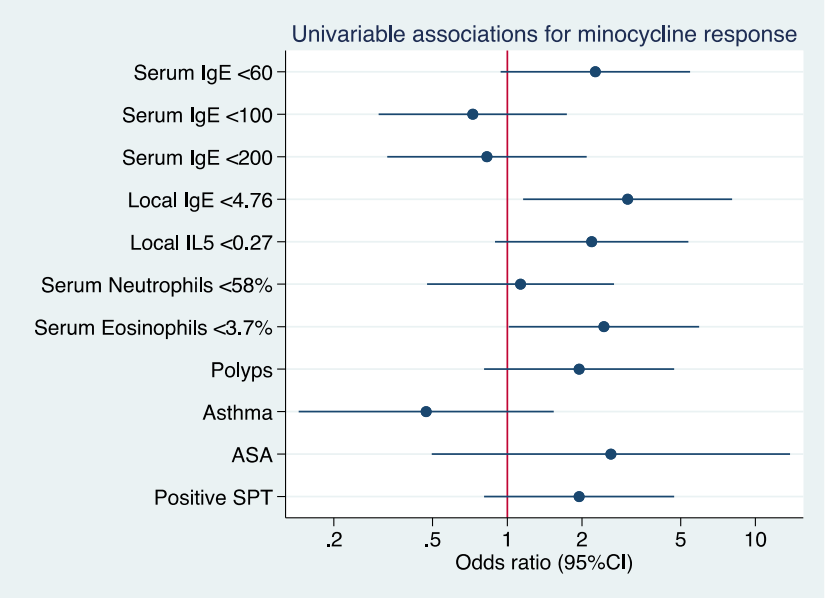

Figure 6 Forest plot showing univariable associations of each variable potentially associated with macrolide response.

Variable	Univariable		Multivariable II	
	OR (95%CI)	P	OR (95%CI)	P
Serum IgE <60 (vs ≥60)	2.26 (0.94 - 5.45)	0.07		
Local IgE <4.76 (vs ≥ 4.76)	3.06 (1.16 - 8.06)	0.02	3.06 (1.16 - 8.06)	0.02
Local IL5 <0.27 (vs ≥0.27)	2.19 (0.89 - 5.36)	0.09		
Serum Eosinophils < 3.7% (vs ≥ 3.7)	2.45 (1.01 - 5.93)	0.05		
Serum neurotrophils <58% (vs ≥58%)	1.13 (0.48 – 2.69)	0.78		
Presence of polyps (vs no polyps)	1.95 (0.81 - 4.7)	0.14		
Asthma (vs no asthma)	0.47 (0.14 - 1.54)	0.21		
ASA sensitivity (vs not)	2.62 (0.5 - 13.79)	0.26		
SPT positive (vs negative)	1.95 (0.81 - 4.7)	0.14		

Table 8 Univariable logistic regression and multivariable logistic regression

Scatterplots of serum total IgE versus local total IgE were used to assess the relationship between these parameters. After restricting the plot and regression line to participants, Spearman's coefficient showed a moderate correlation (rho = 0.6250; P<0.001), demonstrating a monotonically increasing association between serum total IgE and local total IgE (Figure 7).

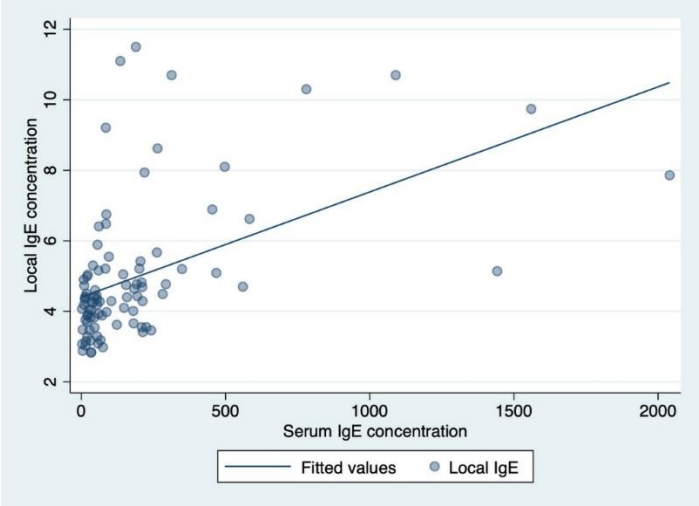

Figure 7 Relationship between local IgE and Serum IgE

To rule out that SPT positive due to the local total IgE from allergic rhinitis patients, we compared local IgE distribution by SPT status. The median, 10^{th,} and 90th percentiles for both groups were very similar (Figure 4). Given the non-normal distribution of the local IgE, we compared the median local IgE levels as a measure of central tendency between the skin prick test positive and negative groups. Quantile regression of the median IgE level showed a median difference in the positive SPT vs. negative SPT groups of –0.216 kU/l (95%CI: -0.85 to 0.52, P = 0.65).

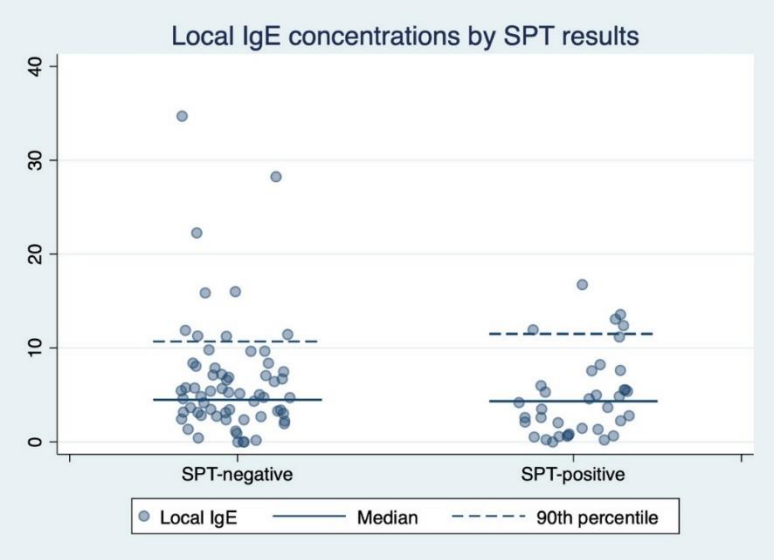

Figure 8 Scatterplot of the local IgE levels, by SPT status

Post hoc analysis

The cut point of serum total IgE at 100 lg/L and 200 lg/L from the previous studies were assessed for the univariable logistic regression. The result showed a non-statistically significant association between serum total IgE=100 lg/L (OR:0.73 95%CI: 0.30 - 1.73, P=0.47) and 200 lg/L (OR:0.83 95%CI: 0.33 - 2.09, P=0.69) with macrolide response.

The sensitivity analysis was done. Thirty-seven participants with a history of positive SPT were excluded, and the logistic regression model re-run. Local IgE remained the only independent predictor of macrolide response.

4.4 Discussion

Low total IgE level in the nasal secretion was revealed as an independent predictive factor for identifying LDM responders in treating CRS. Although Spearman's coefficient analysis showed the relationship between local total IgE level and serum total IgE, serum total IgE cannot predict favorable patients. Although the cut-point for low serum IgE level was changed to 100[8] and 200 lg/L[5, 9], it was still not a significant predictor. These findings suggest that the anti-inflammatory effects of LDM cannot control persistent inflammatory disease in the paranasal sinus caused by type 2 inflammation. Nasal IgE is a reliable biomarker that represents type 2 primary CRS. Its production is located within the mucosa of the paranasal sinus other than regional lymph nodes or lymphoid tissue nearby; therefore, IgE in the systemic blood circulation is not accurate for good patient selection. The airway mucosa of CRSwNP has the inherent capability to produce IgE.

Moreover, not only do IgE-positive B cells reside within the mucosa, but all tools are present locally for affinity maturation by somatic hypermutation, clonal expansion, and class switch recombination to IgE. Local IgE in the absence of systemic IgE was well recognized[1]. It is generally assumed that the increase in the nasal IgE level develops under antigen selection pressure, leading to allergic rhinitis or local allergic rhinitis. Nevertheless, this study's findings showed that the nasal IgE level was not different between patients with and without allergic rhinitis.

Further, when patients with positive allergy tests were removed, a low nasal IgE level still predicted LDM responders. These findings may be explained by the elevations in IgE specific to Staphylococcus aureus enterotoxins, shown in nasal polyp tissue[14]. Chronic colonization and stimulation by superantigens have been hypothesized as a causative or disease-modulating element in CRSwNPs[80]. In contrast, Pratt et al.[81] analyzed IgE sequences from nasal polyp tissue for evidence of antigen selection and showed that IgE antibodies had little influence from antigen selection and were unlikely to be highly specific for antigens.

Serum eosinophils significantly predicted LDM responders by Univariate logistic regression analysis, but it was not significant when multivariate analysis was performed. This finding indicates that low serum eosinophil level was a dependent predictor. Likewise, local IL-5 was not shown as a significant predictor. By rationale, biomarkers and clinical characteristics of type 2 CRS should be used for suggesting appropriate anti-inflammatory agents. The authors hypothesized that low serum eosinophil level, low nasal IL-5 level, a nasal polyp, asthma, and ASA hypersensitivity should be used as clinical predictors. We failed to show significance by statistical analysis. After all, the local IgE production induced by the Th2 cells should be the initial type 2 CRS stage. Consequently, there was a release in local IL-5, which resulted in tissue eosinophilia, serum eosinophilia, and the development of nasal polyps and asthma.

Our findings are in line with a previously published article by Oakley et al.[82] The result of the previous study shows that low tissue and serum eosinophilia and absence of tissue squamous metaplasia may predict a CRS phenotype suitable to a trial of long-term macrolide therapy when surgery and topical therapy has failed. Low tissue and serum eosinophilia and the absence of tissue squamous metaplasia represent the non-type 2 CRS the same as low local total IgE and low serum eosinophils in our study.

This study's clinical applicability is the measurement of local total IgE from the nasal secretion for predicting macrolides responders. The patient does not need the biopsy and the operation for assessing tissue eosinophil or tissue histopathology. A low level of total IgE can predict the chance of macrolides responder preoperative. Besides, low serum eosinophil may be used with low local total IgE to predict macrolide response.

The limitation of this study is the criteria of macrolides responders. There is not a consensus about the suitable criteria for identifying macrolides responders. The criteria of macrolide responder in this study were (1) improvement in SNOT22 of greater than one MCID (9 points)[78] at 12 weeks AND; (2) total nasal symptoms VAS ≤ 5[45] at 12 weeks AND; never requiring rescue medicine at any time point for the whole three months. This criterion is rigorous since the author needs dedicated responders. If we lose the criteria, the number of responders may be higher. Further studies may need to identify the suitable criteria for macrolides responders.

4.5 Conclusion

Low local total IgE from nasal secretion may be a suitable predictor for identifying macrolides responders in treating chronic rhinosinusitis with long-term low dose macrolide therapy. The cut-point of local IgE to maximize the sensitivity and specificity based on ROC curve analysis is 4.76 kU/l.

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AWARD RECEIVED

1. Review paper award from Thai Rhinologic Society for the study ‘Antihistamines for treating rhinosinusitis: a systematic review and meta-analysis’ in 2015

2. 1st winner of research competition at 12th Jakarta International FESS course-workshop 3th -5th March 2017

3. A travelling fellowship award. Prognostic factors of macrolide therapy in treating chronic rhinosinusitis : systematic review and meta-analysis. ERS2018, London, United Kingdom

4. Best oral presentation award (1st prize) at 9th Singapore allergy and rhinology conference 2018