Predictive factors for identifying macrolide responder in treating chronic rhinosinusitis*

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Abstract

Background: Low-dose macrolides (LDM) are anti-inflammatory agents with antineutrophilic activity, but patient selection for LDM therapy in treating chronic rhinosinusitis (CRS) is controversial. This study aimed to assess factors which predict LDM responders.

Methodology: A prospective cohort study was performed. Patients with CRS received roxithromycin (150 mg) once daily for 12 weeks. Nasal secretions and serology were collected. Nine predictors for LDM response were assessed: nasal secretion IgE, nasal secretion IL-5, serum IgE, serum eosinophils, serum neutrophils, nasal polyps, asthma, allergy, and aspirin hypersensitivity, using receiver-operating curve analysis and multivariable logistic regression. Macrolide responders were those with sino-nasal outcome test-22 improvement, symptoms visual analogue scale decreased to ≤5, and no rescue medication.

Results: One hundred CRS patients (mean age 47.4±14.1 years, 45% male) were enrolled. Univariable logistic regression showed local total IgE <5.21; and serum eosinophils <2.2% associated with macrolide response. Multivariate models showed local total IgE maintained an independent association with macrolide response, with an ability to discriminate between responders and non-responders of 63%. Serum total IgE, nasal secretion IL-5, serum neutrophil, nasal polyp, asthma, allergy, and aspirin hypersensitivity showed no association with LDM response.

Conclusions: Low total IgE level in the nasal secretion but not in the serum, predict LDM response.

Key words: macrolides, sinusitis, nasal polyps, anti-inflammatory, total IgE

Introduction

Diversity in chronic rhinosinusitis (CRS) pathogenesis is associated with a broad spectrum of immunologic profiles and T helper (Th) cell type expression[(1)]. Type 2 CRS exhibits Th2-skewed eosinophilic inflammation, with elevated levels of interleukin-5 (IL-5), immunoglobulin E (IgE), eotaxins, and eosinophilic cationic protein. In contrast, non-type 2 shows Th1/Th17-skewed neutrophilic inflammation[(1-3)]. In comprehensive medical treatment for CRS with various inflammation types, anti-inflammatory drugs are the primary medical therapy.

Macrolides are known to have anti-inflammatory and anti-neutrophilic activity[(4)]. Patient selection for low-dose macrolides (LDM) therapy is a controversial issue. The International Consensus Statement on Allergy and Rhinology recommends LDM therapy as an option for patients with both CRS without polyps (CRSsNP) and CRS with polyps (CRSwNP)[(5)]. Conversely, a meta-analysis by our group found benefits of LDM in patients with CRSsNP instead of CRSwNP[(6)]. EPOS 2020 recommends LDM as an optional treatment in patients with non-type 2 primary diffuse CRS[(1)]. The rationale is that LDM should not work for eosi-

nophilic inflammation in type 2 CRS. However, the simultaneous expression of multiple Th cell types has been shown in some patient clusters[7]. Therefore, clinical predictors are required to appropriately select the patients most likely to respond to LDM therapy.

Low serum IgE levels have been recommended for defining LDM responders[8]. However, although this association was found[9], other studies reported discordant results[10,11]. In fact, serum IgE levels may not be an appropriate biomarker, as a growing body of evidence shows local IgE production in rhinosinusitis[12], and specific local IgE can be present in patients who have low serum IgE and negative systemic allergy test results. Eosinophilic inflammation in nasal polyps was shown associated with the increase in nasal secretion IgE, and IL-5 in type 2 CRS[12].

If IgE and IL-5 are produced locally in patients with type 2 CRS[1], then low levels of local IgE and local IL-5 should be more accurate than low serum IgE for identifying LDM responders. This study aimed to assess the discriminative ability of individual predictive factors and combinations of predictive factors for identifying macrolide responders in treating CRS. We hypothesized that low levels of nasally secreted IgE and IL-5 would be a suitable criterion.

Methods

Patient population

Consecutive patients presenting with CRS at the King Chulalongkorn Memorial Hospital from August 2018 to May 2020 were recruited into a prospective cohort. Inclusion criteria were: patients with CRS following the diagnostic criteria recommended by EPOS2012[8] and age between 18-70 years. Exclusion criteria were: macrolide allergy, pregnancy, chronic liver and heart disease, use of systemic steroid in the past 4 weeks and/or topical steroid in the past 2 weeks, previous sinus surgery, neoplasm of nasal and sinus mucosa, cystic fibrosis, systemic vasculitis and granulomatous diseases, immunodeficiency, congenital mucociliary problems, fungal balls and invasive fungal disease, cocaine abuse[8]. They were provided with details about the study that included potential risks and benefits and given ample time to ask questions. All volunteers signed informed consent. The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (number 195/60), and funding was obtained from "The 90th Anniversary of Chulalongkorn University Scholarship".

Data collection

Clinical data collected included nasal obstruction, nasal discharge, 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 a history of an acute exacerbation of bronchoconstriction and other symptoms of asthma after ingesting aspirin or another NSAID. A CT scan of the paranasal sinus was done to confirm the diagnosis of CRS at enrolment. Lund-Mackay CT score[13], the total nasal symptoms based on a visual analogue scale (VAS) of 0-10 (0 was not troublesome and 10 was worst thinkable troublesome)1, and the Thai version of the sino-nasal outcome test 22 (SNOT-22)[14] were used to assess CRS disease severity. Nasal polyps were evaluated by nasal endoscopy. Serology was done to assess serum total IgE, eosinophils and neutrophils. Allergy status was assessed with the skin prick test using fifteen common local aeroallergens. Nasal secretions were obtained by inserting a 1x3 cm, dehydrated sponge composed of hydroxylated polyvinyl acetate (Merocel, Medtronic Inc., Minneapolis, MN, USA), into each middle meatus by nasal endoscopy without an anaesthetic agent 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 [15]. The level of total IgE was assessed using a fluoroenzyme immunoassay (ImmunoCAP, Phadia, Sweden) and the concentrations of IL-5 were determined by an Enzyme-linked immunosorbent assay (ELISA) (Human IL-5 ELISA Kit, Abcam, UK) according to manufacturer's instructions.

LDM therapy

Patients received 150 mg of roxithromycin once daily for 12 weeks. They were asked to rinse their noses with saline irrigation twice a day. Concomitant drugs were not allowed. There were three follow-up visits at 4 weeks, 8 weeks, and 12 weeks; total nasal symptoms VAS was evaluated at baseline and every follow-up visit. If the patients had total nasal symptoms by VAS greater than 7 at any follow-up visit [8], roxithromycin was discontinued, and they were defined as macrolide non-responders. Then rescue medications were given to the non-responders, including intranasal corticosteroids, oral corticosteroids, or oral antibiotics according to disease severity. The non-responders finished the study and received standard medical treatment regimen tailored to each patient's needs.

Predictors for macrolide responders

Nine potential predictors of macrolide responders assessed in this study: nasal secretion of total IgE, nasal secretion of total IL-5, (3) serum total IgE, (4) serum eosinophil, (5) serum neutrophil, nasal polyps, asthma, positive allergy test for allergic rhinitis, and aspirin hypersensitivity. At the 12-week follow-up visit, patients were categorized as either macrolide responders or non-responders. The criteria for macrolide responders were (1) improvement in SNOT22 of greater than one minimal clinically important difference (MCID; 12 points)[16] at 12 weeks AND; (2) total nasal

symptoms VAS ≤ 5[1,8] at 12 weeks AND; never requiring rescue medicine at any time point for the entire three-month study duration.

Statistical analysis

Power calculations were based on the assumption that the proportion of responders and non-responders in the study sample would be approximately equal, and the presence of a negative prognostic factor would be present in approximately 75% of non-responders versus 40% of responders. Under these assumptions, enrolling 96 patients would provide 90% power to detect this difference at a 2-sided significance level of 5%. The sample size was inflated by 8% to account for possible losses to follow-up. Statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX, USA). Associations between continuous biomarkers were explored graphically, by whether or not participants were macrolide responders. Due to non-normal distributions and clustering of some variables at low values, we compared categorical and continuous distributions by response group using a Fisher's exact or Wilcoxon rank sum or test, respectively. Spearman's rank coefficient (rho) was to quantitate monotonic relationships between continuous parameters. A receiver operating characteristic curve (ROC) was generated, and continuous predictors were categorized at a cut point, which maximized the sum of the sensitivity and specificity, and therefore the correct classification rate (Youden's index) [17,18]. The performance characteristics, including sensitivity, specificity, and likelihood ratios, were derived at this cut point. In addition, we calculated the area under the ROC curve (AROC) and 95% confidence intervals (95%CI) as a measure of predictor discrimination. Univariable logistic regression was used to calculate diagnostic odds ratios for each dichotomized biomarker and other potential predictors, and multivariable logistic regression was then used to select a model for identifying macrolide responders in treating CRS. We assessed two models: the first adjusting for all parameters significant in the univariate analysis at P<0.1. The second a backward stepwise selection where the variable with the highest (least-significant) P-value was dropped until all remaining terms were significant at P<0.1. The multivariate models were compared using Akaike's and Bayesian information criteria (AIC and BIC); with lower values of these parameters indicating a preferable model. The Hosmer and Lemeshow test was used to assess model goodness of fit. 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.

Results

Demographic and disease characteristics at baseline

One hundred and twelve patients were assessed for eligibility, five patients were not eligible due to previous sinus surgery history, and two patients declined to enroll since they could not commit to attending monthly follow-up visits. One hundred and five patients with CRS enrolled in the study; 5 patients failed to complete the study (Figure 1). A total of 100 patients (mean age: 47 ± 14.1 years, 45% male) with CRS were included in the analysis. Twenty-two percent had asthma, 38% were atopic, and 6% had aspirin sensitivity. Nasal polyps were observed in 37% on nasal endoscopic examination, 91% complained of nasal obstruction, 94% had nasal discharge, 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 ± 18.8, and Lund Mackay CT score was 12.38 ± 4.3.

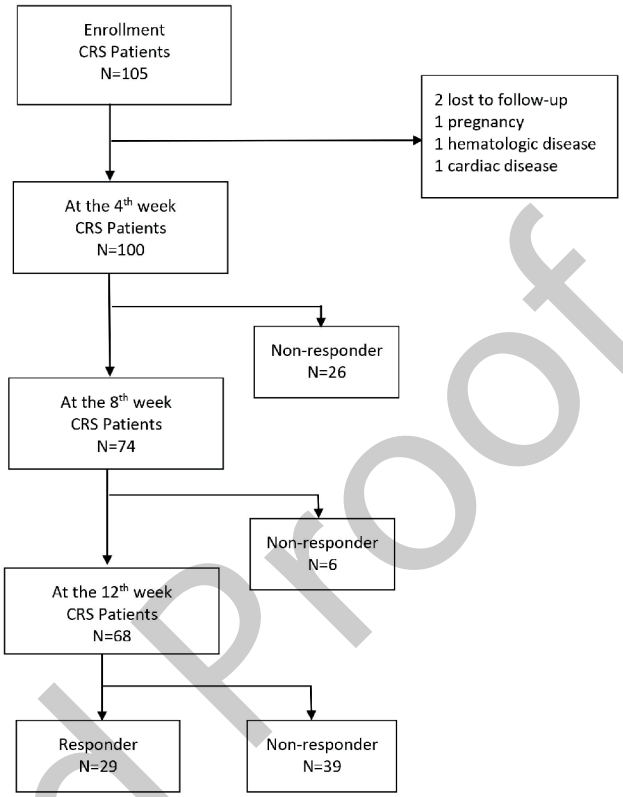

Figure 1. Flow diagram of the study.

Number of patients with macrolide response

Twenty-six patients had VAS > 7 at the week 4 visit and were classified as macrolide non-responders. They discontinued roxithromycin and received rescue medication. At weeks 8, 74 patients continuing on study attended their second follow-up. Six patients had VAS > 7, meeting macrolide non-responder criteria and finished the study. At the final study follow-up, 29 patients met the macrolide responders' criteria, giving a total of 71 non-responders over the study (Figure 1).

Biomarker distributions and characteristics associated with macrolide response

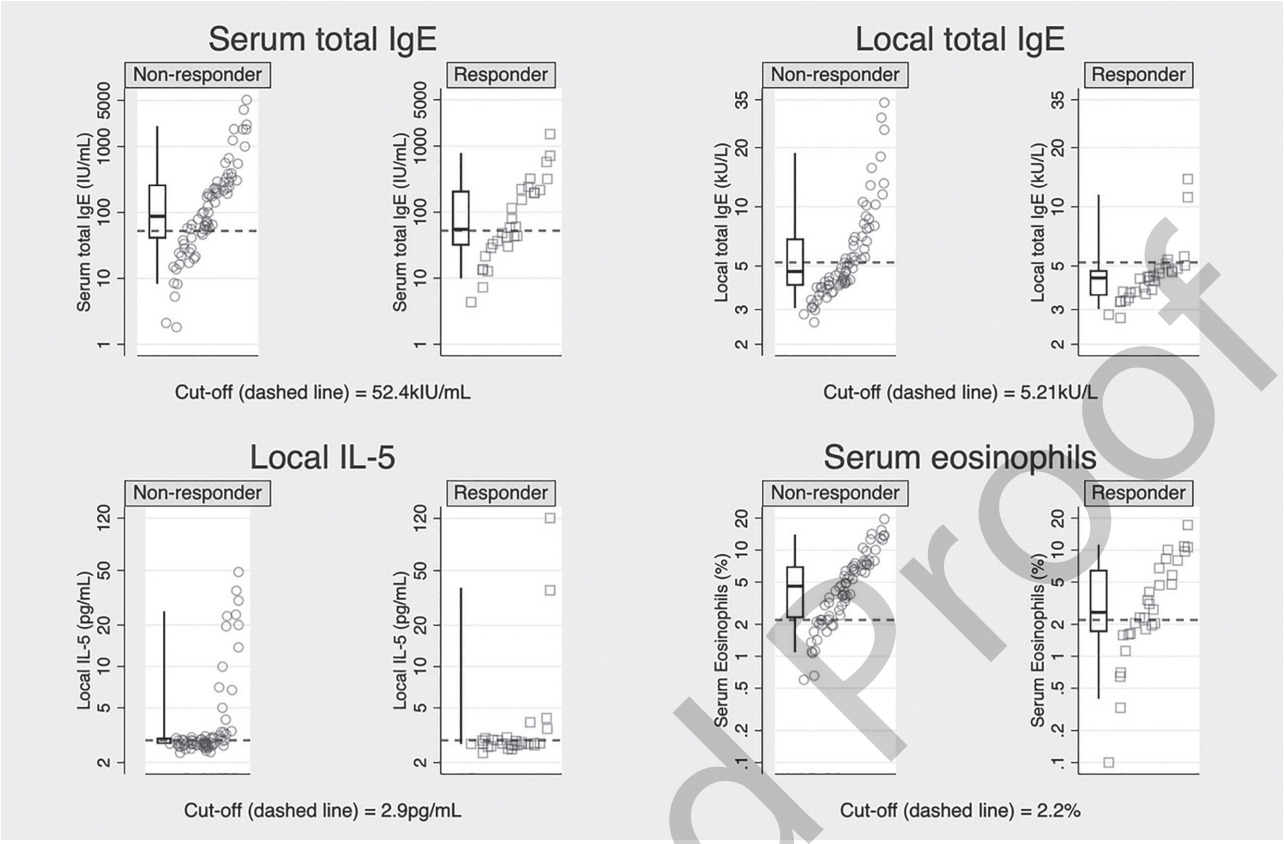

Figure 2. Quantile plot of biomarker distributions. Quantile plot of biomarker distributions with cumulative probability scales on the horizontal axis. Boxes show median and quartiles and whiskers extend from the 5th to the 95th percentile. Fifty percent of the data points for each variable lie within each box; 95% of each of the data points for each variable lie within between the limits of the whiskers.

Serum and local IgE distribution and serum eosinophils distributions showed skewed distributions, with higher levels across all quartiles in the non-responders versus responders (Figure 2). Median (IQR) serum total IgE levels were 87.3 (40.4-264) IU/mL in non-responders, and 54.8 (31.3-209) IU/mL in responders (P=0.23). Median local total IgE level in non-responders were 4.69 (3.98-6.89) kU/l and 4.34 (3.54-4.75) kU/l in responders (P=0.045), and median serum eosinophils were 4.6 (2.3-7.0)% in non-responders versus 2.6 (1.7-6.5)% in responders (P=0.08). Serum neutrophil distribution was similar across both groups: median (IQR) level in non-responders was 56.6 (49.6-64.6)% versus 56.7 (50.8-64.5)% in responders (P=0.90). Seventy-six percent

Table 1. The area under the ROC curve (AROC), sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio of all dichotomized biomarkers and other categorical predictor variables.

Variable (dichotomized)	AROC (95%CI)	Sensitivity	Specificity	LR+	LR-
Serum IgE <52.4	0.60 (0.49 - 0.71)	48.28	71.83	1.71	0.72
Local IgE <5.21	0.65 (0.57 - 0.73)	89.66	39.44	1.48	0.26
Local IL5 <2.9	0.54 (0.46 - 0.63)	82.76	43.00	1.13	0.64
Serum eosinophils <2.2%	0.62 (0.51 - 0.72)	44.83	78.87	2.12	0.70
Serum neutrophils <60%	0.52 (0.42 - 0.63)	65.52	39.44	1.08	0.87
Presence of polyps	0.58 (0.47 - 0.69)	48.28	67.61	1.49	0.77
Asthma	0.44 (0.36 - 0.52)	13.79	74.65	1.15	0.54
ASA sensitivity	0.53 (0.47 - 0.59)	10.34	95.77	2.45	0.94
SPT positive	0.58 (0.47 - 0.69)	48.28	67.61	1.49	0.77

Table 2. Univariable and multivariable logistic regression showing odds ratios (OR) and adjusted odds ratios (aOR) for associations with macrolide response.

Variable	Univariable		Multivariable model 1*		Multivariable model 2*	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Serum IgE <52.4 (vs ≥52.4) kU/L	2.38 (0.97 - 5.81)	0.06	1.25 (0.46 – 3.35)	0.66		
Local IgE <5.21 (vs ≥5.21) kU/L	5.64 (1.55 – 20.42)	0.008	4.35 (1.11 – 17.10)	0.04	4.76 (1.29 - 17.58)	0.02
Local IL5 <4.5 (vs ≥4.5) pg/mL	2.74 (0.57 – 13.13)	0.20				
Serum Eosinophils < 2.2 (vs ≥ 2.2) %	3.03 (1.19 – 7.66)	0.02	2.30 (0.86 – 6.11)	0.10	2.39 (0.91 – 6.25)	0.08
Serum neutrophils <60 (vs ≥60) %	1.23 (0.50 – 3.04)	0.64				
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				
			AIC = 115.82 BIC = 126.24 AROC = 0.71 (95%CI 0.59 – 0.82) HL-GOF P = 0.23		AIC = 114.01 BIC = 121.82 AROC = 0.71 (95%CI 0.61 – 0.82) HL-GOF P = 0.52	

* Multivariable model, adjusts for all factors significant in univariate analysis at P<0.1. Multivariate model 2 was based on backwards stepwise selection until all remaining terms were significant at P<0.1. AIC = Akaike's information criteria, BIC = Bayesian information criteria, AROC = Area under the ROC curve, HL-GOF = Hosmer and Lemeshow Goodness of Fit Test P-value.

of local IL-5 levels were below the assay lower limit of quantitation; 52/79 (73%) non-responders and 24/29 (82%) responders (P=0.44). The percentage of non-responders and responders with aspirin allergy, asthma, nasal polyps and positive skin prick tests were 4 vs 10% (P=0.35), 25 vs 13% (P=0.29), 32 vs 48% (P=0.17) and 32 vs 48% (P=0.17), respectively.

Serum total IgE showed a high degree of correlation with local total IgE (rho=0.63; P<0.001) and a moderate correlation with serum eosinophils (rho=0.33; P<0.001). Local total IgE also showed a moderate correlation with serum eosinophils (rho=0.34; P<0.001), and serum eosinophils showed a strong negative correlation with serum neutrophils (-0.53; P<0.001).

Each of the predictors was dichotomized at a cut-point which maximized the sensitivity and specificity. The serum total IgE, local total IgE, local IL-5, serum eosinophils, and serum neutrophils were 52.4 IU/mL, 5.21 kU/l, and 2.90 pg/ml, 2.2%, and 60%, respectively. The AROC, sensitivity, specificity positive likelihood ratio (LR+), and negative likelihood ratio of all potential predictors are shown in Table1.

Univariable logistic regression was conducted with the dichotomized biomarkers and other potential categorical predictors of response. Only local total IgE<5.21 kU/l (OR: 5.64, 95%CI: 1.55–20.42, P=0.008) and serum eosinophils<2.2% (OR:3.03, 95%CI 1.19-7.66, P=0.02) showed a statistically significant association with macrolide response (Table 2). In a model adjusting for serum IgE <52.4 IU/mL and serum eosinophils <2.2%, local IgE was the only independent predictor. After dropping serum IgE, the discriminative power of the model with local IgE and serum eosinophils was unchanged (AROC for both=0.71). The Hosmer and Lemeshow test showed adequate goodness of fit. In this model the odds ratio for local IgE<5.21 kU/l for macrolide response was 4.76 (95%CI 1.29-17.58; P=0.02) and for serum eosinophils<2.2% was 2.39 (95%CI 0.91-6.25; P=0.08). Based on this model, the probability of macrolide response was 8% (95% CI 2.6-23) in a participant with both local IgE and serum eosinophils above the cut-point, 30% (95%CI 19-45) in a participant with local IgE <5.21 kU/L and serum eosinophils ≥2.2%, and 51% (95%CI 33-69) in participants with local IgE <5.21kU/L and serum eosinophils <2.2%.

To investigate whether local total IgE from allergic rhinitis patients was related to SPT, we compared local IgE distribution by SPT status. The median, 10th, and 90th percentiles for both groups were very similar (Figure 3). 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 –0.16 kU/l (95%CI: -0.85-0.52, P=0.65). Lastly, in a sensitivity analysis, restricting multivariate model2 to those who SPT-negative, local IgE remained the only independent predictor of macrolide response.

Post hoc analysis

Cut-points of serum total IgE of 200 µg/L[8,9] and 100 IU/mL[10] identified in previous studies of macrolide non-responders were assessed for an association with macrolide response using uni-

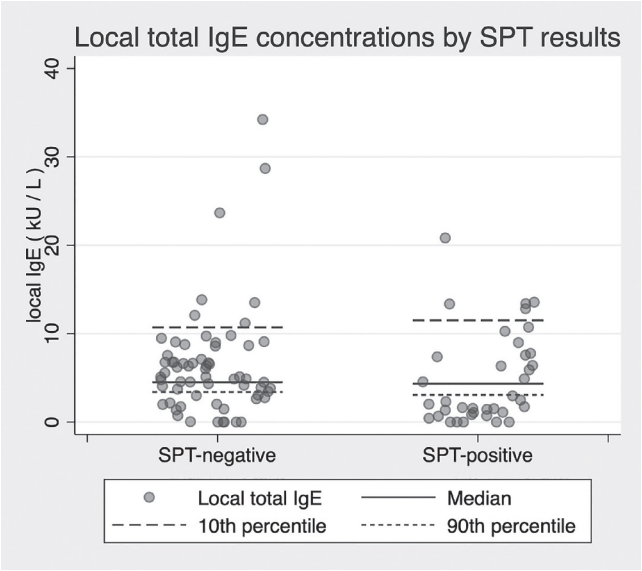

Figure 3. Scatterplot of local total IgE levels, by skin prick test status.

variable logistic regression. The result showed no associations between macrolide response with serum total IgE <200 µg/L (OR:0.63 95%CI: 0.26 -1.50, P=0.30) and serum total IgE <100 IU/mL (OR:0.73 95%CI: 0.30-1.73, P=0.47).

Discussion

Low total IgE level in the nasal secretion was an independent factor for identifying LDM responders in treating CRS. Although we found correlation in the local total IgE level and serum total IgE, serum total IgE was not associated with response when included in a model together with local total IgE. Even changing the cut-point for low serum IgE level to 200 µg/L[8,9] and 100 IU/ml[10] identified in other studies, the alternative cut-points still showed no association with LDM response. 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 total IgE is a reliable biomarker that characterizes type 2 primary CRS. It is produced within the paranasal sinus mucosa rather than regional lymph nodes or lymphoid tissue nearby; therefore, IgE in the systemic blood circulation cannot accurately predict favorable macrolide response. The airway mucosa of CRSwNP has the intrinsic capability to produce IgE. Moreover, IgE-positive B cells reside within the mucosa, in addition to all tools needed for affinity maturation by somatic hypermutation, clonal expansion, and class switch recombination to IgE. Local IgE in the absence of systemic IgE is well recognized[12]. 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, our current study shows that the nasal IgE level was not different between CRS patients, with or without allergic rhinitis. Further, when patients with positive allergy tests were removed, low levels of nasal IgE still predicted LDM responders. These findings may be explained by the elevations in IgE specific to *Staphylococcus aureus* enterotoxins, shown in nasal polyp tissue[19]. Chronic colonization and stimulation by superantigens have been hypothesized as a causative or disease-modulating element in CRSwNPs[20]. In contrast, Pratt et al.[21] 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 in univariable logistic regression but was not significant after adjusting for local IgE levels in multivariable analysis. This discrepancy is partly due to the moderate correlation observed between these two variables, but the association with low eosinophils was weaker than that observed with local IgE. Likewise, local IL-5 did not predict LDM response. The logical extension of these observations is that biomarkers and clinical characteristics of type 2 CRS should be used for selecting the appropriate anti-inflammatory agent. Local IgE production induced by the Th2 cells would occur in the initial stages of type 2 CRS. Consequently, the release of local IL-5 would result in tissue eosinophilia, serum eosinophilia, and nasal polyps and asthma development. However, the only independent predictor in our model was found to be low local IgE. Neither asthma history nor ASA hypersensitivity was negative predictors. The low number of ASA hypersensitivity patients in this study (6%) is mostly insufficient to show a relationship with response. Although asthma is associated with type 2 inflammatory patterns, this association varies according to other key cytokines involvement. Tomassen et al.[7] classified patients with CRS into ten clusters based on 14 biomarkers and matched these ten clusters with phenotypes including asthma. Patients with type II CRS had asthma with a prevalence ranging from 20% to 60% and related to other biomarkers. Patients with increased IgE level had varied level of IL-5. Our study showed that IL-5 was not a significant negative predictor, and neither was asthma. Our findings are consistent with a previously published case-control study. Oakley et al.[22] recruited twenty-eight recalcitrant CRS patients to receive 3-months of clarithromycin therapy. Macrolide responders with near-normal endoscopy had low serum (<0.39 x10^9/L) and low tissue (<10/ HPF) eosinophilia and absence of tissue squamous metaplasia by histopathology. These findings suggest that macrolide response was associated with non-type 2 inflammation. Likewise, this study showed that serum IgE level, serum neutrophilia, the presence of nasal polyps, asthma, and allergy failed to predict macrolide response. However, this study used the histopathology report to identify postoperative patients suitable for LDM therapy but our study aimed to identify CRS patients suitable for LDM therapy before endoscopic sinus surgery. Based on our study findings, and those reported by Oakley et al.

[22] showing that serum IgE did not predict macrolides responders, recommendations for clinical practice guidelines should be reconsidered. The recommendation for using low serum IgE levels was based on a study by Wallwork et al. [9] Nevertheless, Haxel et al. [10] found no difference in macrolides response between patients with low (<100 IU/mL) and high serum IgE levels. Likewise, a study reported by Maniakas et al. [11] gave azithromycin to patients who failed to 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).

In clinical practice, we suggest that clinicians should bear in mind that CRS is a heterogeneous disease; therefore, an individual patient's inflammatory pattern should be assessed before selecting appropriate anti-inflammatory agents. Nevertheless, corticosteroids are the most potent anti-inflammatory drugs, which brings the maximum benefits to patients with type 2 CRS. Long-term LDM is the other medicine with anti-inflammatory effects selected for patients with non-type 2 CRS. Persistent inflammation in patients with primary CRS can be controlled with LDM therapy before considering endoscopic sinus surgery. Based on the findings of our study, low IgE level in the nasal secretion, not in the serum, predicts LDM responders. However, collecting nasal secretions for IgE measurement is not practical in real-life practice. Although not an independent predictive factor in our multivariate logistic regression, serum eosinophil level is more practical and may be useful for patient selection.

Our study has a number of limitations. First, no consensus exists for the classification of macrolides responders, and the relationship between clinical variables and macrolide response is therefore confounded by the criteria used to classify response. To mitigate this limitation, our study established specific criteria to ensure that the patients who met these predetermined criteria were actual LDM responders. After four weeks of treatment, LDM responders should not have severe symptoms, defined as total severity on visual analog scale of less than 7[8]. At 12 weeks, LDM responders should have clinical improvement, with clinically-insignificant symptoms only, when assessed by a validated disease-specific questionnaire with a clinical significance[16]. Symptoms not affecting the quality of life were defined by total severity on visual analogue scale of less than 5[8]. In addition, LDM responders should not have required rescue medicine over the past three months[8]. The authors acknowledge that more clinical variables may show a statistically significant association with the outcome, if less stringent definitions of are applied. Second, the prevalence of responders in our sample was only 29%, which partly limits our ability to derive predictive models. Nevertheless, in various sensitivity analyses, local IgE was the only factor consistently shown to independently predict macrolide response. Further studies exploring the immunological profile of these patients with low levels of local IgE may give further insights into the pathogenesis of this condition, and other possible factors which could predict response.

Conclusion

Low total IgE level in the nasal secretion, but not in the serum, predicts response to long-term LDM. The mucosa of the paranasal sinuses has the intrinsic capability to produce IgE in patients with CRS. Anti-inflammatory effects of LDM bring clinical benefits to patients with non-type 2 CRS. Nevertheless, we do not suggest measuring total IgE level in the nasal secretion in practice due to its low specificity.

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Author contribution

KSE: study design, data collection, data analysis, drafting the article, final approval. SJK: study design, data analysis, editing the article. SA: data collection, editing the article. SC: data collection, editing the article. JK: data collection, editing the article. JW: data collection, editing the article. KSN: conception, study design, data analysis, drafting the article, final approval.

Conflict of interest

Kornkiat Snidvongs received Honoraria for speaking at symposia from Merck Sharp & Dohme, Mylan, and Menarini.
Kachorn Seresirikachorn, Stephen J Kerr, Songklot Aeumjaturapat, Supinda Chusakul, Jesada Kanchanaumporn, Jongkonnee Wongpiyabovorn declare that they have no conflict of interest.

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