Low-dose macrolides for treating pediatric rhinosinusitis: A retrospective study and literature review

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Abstract

The effects of low-dose macrolide (LDM) therapy on pediatric chronic rhinosinusitis (CRS) patients are unknown. This study aimed to assess the effectiveness of LDM for treating pediatric refractory CRS. A retrospective study was conducted by a medical chart review. Pediatric CRS patients (age <15 years) who received LDM after standard medical treatments failure between 2013 and 2019 were identified. The LDM treatments with any macrolide agents, doses, and regimens were included. Any co-interventions were allowed. Duration of the LDM therapy was ≥6 weeks. Outcomes were the total nasal symptoms by the visual analogue scale (TNS), presence of individual symptoms, physician-assessment nasal discharge and adverse events. Six patients (67% male, mean age 7±3.4 years) were assessed. All patients had failed to intranasal steroids and nasal saline irrigation but continued. The addition of LDM significantly improved TNS (mean difference ± standard deviation 5.83 ± 1.33; 95% confidence interval 4.44–7.23, p< 0.001). At the end of treatment, the numbers of patients with individual symptoms were decreased: nasal obstruction (100%–67%), rhinorrhea (83%–50%), hyposmia (50%–0%), cough (100%–33%), and physician-assessment thick mucoid discharge (33%–0%). No patients had facial pain. One patient reported mild tolerable nausea. Preliminary findings of this study showed some beneficial effects of LDM added to intranasal steroids and nasal saline irrigation in pediatric CRS after standard treatments failure. The beneficial effects included the improvements of the TNS and individual nasal symptoms and decrease in thick mucoid discharge.

Keywords

Pediatrics, rhinosinusitis, macrolides, chronic inflammation, steroid

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Introduction

Intranasal steroids, together with nasal saline irrigation, have been the cornerstone of treatment of chronic rhinosinusitis (CRS).[1] Refractory CRS is common in pediatric patients,[2] 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,[2,3] 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[1]; nevertheless, there is no evidence

supporting the use of these therapeutic options.[4] 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,

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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.[5–7] In contrast, most pediatric refractory CRS are chronic rhinosinusitis without nasal polyps (CRSsNP) and associate with Th1/Th17-skewed neutrophilic inflammation with elevated levels of interferon-γ, transforming growth factor (TGF)-β, IL-17, myeloperoxidase, IL-6, IL-8, and IL-1β.[8] When choosing anti-inflammatory agents to the individual patient, patients with CRSwNP are acknowledged corticosteroid responsive[9] and should respond to the anti–matrix metalloproteinase (MMP) 9 property of doxycycline,[10] 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.[11]

Currently, the recommendation of LDM therapy regarding patient selection is controversial. While two international guidelines suggest LDM therapy for both CRSsNP and CRSwNP,[1,12] another guideline does not suggest LDMs at all.[13] A recent systematic review and meta-analysis revealed that LDM therapy is effective only in CRSsNP.[14] 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.

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 LDMs after standard medical treatment failure between 2013 and 2019 were identified. The uncontrolled CRS was defined as (1) had at least three 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.[1] Standard medical treatment[1] 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, and 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,[1] (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 (TNSs) 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 LDMs 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

Table 1. Demographic data of the patient population.

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.

was less than 0.05. Statistical analyses were performed using SPSS v 22.0 (Statistical Package for the Social Sciences, Chicago, IL).

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 1.

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 2.

The TNSs were significantly improved after the addition of LDM therapy (mean difference $\pm$ SD: 5.83 ± 1.33, 95% confidence interval (CI): 4.44–7.23, $p < 0.001$). LDMs decreased the numbers of patients who had symptoms and signs, including nasal obstruction (from 100%–67%), rhinorrhea (from 83%–50%), hyposmia (from 50%–0%), cough (from 100%–33%), and thick mucoid discharge (by physician assessment; from 33%–0%). No patient had facial pain and purulent discharge (by physician assessment) neither pretreatment nor at the end of treatment. One patient reported mild, tolerable nausea. Data are displayed in Table 3.

Discussion

Literature review

Inflammatory pattern of pediatric CRS. Pediatric refractory CRS associate with Th1/Th17-skewed neutrophilic inflammation.

The levels of the cytokine TNF-α, the anti-microbial peptide human beta-defensin 2, and neutrophil-released calprotectin in nasal lavages of pediatric patients with CRS were found higher than those in healthy controls.[15] Chan et al.[8] 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,[16] 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.[17,18] 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. Co-immunofluorescence 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 and 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.[19] demonstrated an increase in 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. In addition, hypertrophic adenoid is a reservoir of bacteria. Shin et al.[20] assessed a correlation between adenoid tissue bacterial culture, rhinosinusitis severity, and adenoid size. The bacterial isolation rate increased significantly according to rhinosinusitis severity, especially *Haemophilus influenzae* and Streptococcus pneumoniae with regardless of adenoid size. Zuliani et al.[21] found dense bacteria biofilm covering

Table 2. Summary of medical therapy.

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	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 3. Clinical effectiveness of LDM therapy.

	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.

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.[21] 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.[22] found higher levels of the T cell activation marker, soluble interleukin-2 receptor (sIL-2R), and higher levels of cytokines associated with tissue remodeling including TGFβ-1, 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.[23] 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 and 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.[24] The mechanism of anti-neutrophilic action of LDMs is associated with the suppression of the production of IL-8 and TNF-α.[8,25–28]

Furthermore, the LDMs have been shown to decrease mucus formation, secretion, and viscosity.[8,29,30] 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 on the management of cystic fibrosis and diffuse panbronchiolitis.[31,32] Based on these rationales, LDM therapy with anti-neutrophilic 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,[33] (2) 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 were not only statistically significant but also clinically meaningful. The average score of symptom improvements was around 6 of the maximum score of 10. Individual symptoms were absent in most patients. The physician assessment nasal discharge, including thick mucoid and purulent discharge, was 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,[8,34,35] and among pediatric patients with CRS, the inflammatory patterns were more neutrophilic than eosinophilic inflammation.[8] 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.[14] 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.[14] 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: 1.29–9.60) and there was no cardiac adverse effect reported in any patients.[14] 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 does 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 because there was no study in pediatric from the recent Cochrane review.[36] 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.[36]

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 on 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 is required to demonstrate evidence of the additional effects of LDMs on pediatric patients. Co-interventions should not be allowed to determine the effects of individual LDM therapy.

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 the TNS 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.

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Declaration of conflicting interests

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Ethics approval

Ethical approval for this study was obtained from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (approval number 085/62).

Informed consent

All analyzed data were devoid of identifiable personal information. Patient consent is not required for accessing the electronic medical record. The data are allowed to use for academic purpose only after proof by the institutional review board (IRB) and the Director of King Chulalongkorn Memorial Hospital. The IRB approved this study (IRB 085/62) and waived the requirement of informed consent.

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