Pharmacotherapy of Chronic Rhinosinusitis with a Focus on Clarithromycin: An Expert Opinion

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Abstract

Chronic Rhinosinusitis (CRS) is frequently distinguished as persistent symptomatic inflammation of the nasal and sinus mucosa and is recognized as one of the most common chronic diseases, with high incidence rate. It has a major impact on overall quality of life. Although, the etiology and pathogenesis of CRS are not clearly understood, there are several hypotheses on CRS etiology and pathogenesis. The presence of biofilms and bacterial infection, as well as fungal infection, allergy, environmental pollutants, and smoking are considered as a possible environmental factors which are involved in etiology of CRS. Over the past few years, the presence of biofilms is indicated in more than 65% of chronic infections in humans. The most important goals of treatment in CRS include suppression of the infection, reduction of sinonasal inflammation, and maintenance of patent sinonasal passage drainage. CRS is generally treated with medical and surgical therapy. Antibiotics play a major role in the treatment of CRS and are often used to reduce the infectious component of CRS. Macrolide antibiotics are considered as a choice of treatment option as they have anti-inflammatory and immunomodulatory properties in addition to usual antimicrobial effects. Clarithromycin is one of the macrolide which has shown beneficial effects for treating CRS. Various studies indicated that long term use of clarithromycin is effective in the treatment of CRS with good tolerability profile. The present review suggests that clarithromycin can be used as treatment of choice in the treatment of CRS.

Background

Chronic rhinosinusitis (CRS) is frequently linked with significant morbidity and healthcare expenditure.¹ CRS is usually defined as persistent symptomatic inflammation of the nasal and sinus mucosa. Chronic rhinosinusitis is considered as one of the most common chronic diseases, with high incidence (15%) in some populations.² It is not a distinct disease entity but is an ‘umbrella’ term for a number of pathologic conditions with definite immunopathological mechanisms.³ An estimated 134 million Indians suffer from CRS, as per the National Institute of Allergy and Infectious Diseases.⁴ Despite appropriate medical therapy, a subset of patients with CRS continue to be symptomatic and eventually undergo endoscopic sinus surgery (ESS).³ In the United States, National Health and Nutrition Examination Survey data predicted the prevalence of CRS between 13 and 17%. In Europe, it was estimated to be 10.9%.⁴

For diagnosis of acute and chronic rhinosinusitis, five major symptoms; i.e. facial congestion/fullness; facial pain/pressure/fullness; nasal obstruction/blockage; purulent anterior/posterior nasal drainage (may be non discoloured or non-purulent); and hyposmia/anosmia should be considered (Canadian Clinical Practice Guidelines). At least two symptoms must be present for at least 8–12 weeks, as well as confirmation of disease can be done with endoscopy or CT scan.³

Though, the exact pathogenesis remains poorly understood, this inflammatory condition is commonly divided into two phenotypes based on the presence or absence of nasal polyps i.e. CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSsNP) (Figure 1). CRSsNP includes a varied group of disorders which can be different but yet can overlap in etiology and typically signifies up to 60% of CRS cases. CRSsNP is a more definite immunological disease. Type 1 T-helper (Th2) dominance with excess, Interleukin-5 (IL-5), Interleukin-4 (IL-4), and Interleukin-13 (IL-13) expression is observed in this subtype.¹

Thus, CRS remains a highly prevalent disease with a major impact on overall quality of life. Current management techniques mainly target to reduce inflammation with the goal of restoring normal sinus physiology. The treatment options for CRS include, antibiotics, nasal decongestants, topical nasal steroids and/or oral steroids, saline irrigation and surgery. Macrolide antibiotics are a common choice of treatment option for both, CRSsNP and CRSsNP.² In this article we review the main characteristics of CRS, describe the current treatment methods and role of macrolide antibiotic, clarithromycin, in CRS management.

Etiology and Pathogenesis

The etiology and pathogenesis of CRS are not clearly understood. There are several hypotheses on CRS etiology and pathogenesis, which are discussed in Table 1. These hypotheses usually comprise excessive host response to fungi, aspirin intolerance due to defects in the eicosanoid pathway, staphylococcal superantigen resulting in exotoxin effects including tissue damage, coordinated mechanical barrier and the innate immune response of the sinonasal mucosa, defects in the immune barrier and biofilms...
The etiology of CRS involves many factors. In CRS, the interaction between systemic, local host, and environmental factors results into sinus inflammation. Systemic factors include genetic diseases such as cystic fibrosis, conditions causing immunodeficiency, autoimmune disease, idiopathic conditions such as Samter’s triad (aspirin exacerbated respiratory disease), and acid reflux. Local host factors include sinonasal anatomic abnormalities, iatrogenic conditions such as scarring from prior sinus surgery, neo plasm, or the presence of a foreign body, among others. The presence of biofilms and bacterial infection, as well as fungal infection, allergy, environmental pollutants, and smoking are considered as a possible environmental factors. Over the past few years, the presence of biofilms is indicated in more than 65% of chronic infections in humans.7

**Biofilms**

Bacteria can be found in nature in two distinct forms; biofilm and planktonic. Biofilm comprises of a group of micro-organisms in which cells stick to each other on a surface of extracellular polymeric substance (EPS). Biofilms are micro-organisms in which bacteria produce an extracellular polymeric substances (EPS) such as proteins (<1-2%) including enzymes, DNA (<1%), polysaccharides (1-2%) and RNA (<1%), and in addition to these components, water (up to 97%) is the major part of biofilm which is responsible for the flow of nutrients inside biofilm matrix. The example of biofilm has been shown in the Figure 2a.57

The progression of a microbial biofilm is a complex process. The different steps in biofilm life cycle are shown in Figure 2b. Biofilm formation usually has following important steps (a) attachment initially to a surface (b) formation of micro-colony (c) three dimensional structure formation (d) biofilm formation, maturation and detachment.7

- Attachment: When a bacterium cell reaches close to near some surface/support; its motion slows down and it make a reversible connection with the surface and/or already adhered other microbe to the surface.
- Micro-colony formation: When the binding between bacteria and surface becomes stable; it results into the formation of micro-colony.
- Three-dimensional structure formation and maturation: After formation of micro-colony, expression of certain biofilm related genes take place. These gene products are important material for the main structure material, EPS, of biofilm.

**Table 1: CRS etiology and pathogenesis hypotheses**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Description</th>
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<tbody>
<tr>
<td>Fungal Hypothesis</td>
<td>Excessive host response to fungi</td>
</tr>
<tr>
<td>Superantigen hypothesis</td>
<td>Staphylococcal superantigen resulting in exotoxin effects including tissue damage</td>
</tr>
<tr>
<td>Biofilm hypothesis</td>
<td>Defects in biofilms formation</td>
</tr>
<tr>
<td>Eicosanoid hypothesis</td>
<td>Aspirin intolerance due to defects in the eicosanoid pathway</td>
</tr>
<tr>
<td>Immune barrier hypothesis</td>
<td>Host factors defects in the immune barrier</td>
</tr>
</tbody>
</table>

Almost 99% of bacteria have ability to form biofilm. When bacteria bind to a surface, they produce EPS; which helps to form biofilm. Though, the biofilm forming capability has been reported in large number of bacterial species such as H. influenza, P. aeruginosa, S. aureus, S. epidermidis, E. coli, E. cloacae, K. pneunoniae, it was observed that the bacterial species, H. influenza, has the ability to escape from human immune system.7

Biofilm antibiotic resistance level and key factor responsible for that may differ among different settings. It was observed that the resistance posed by the adhered bacteria or biofilms may have some intrinsic mechanisms like limited diffusion, enzyme causing neutralizations, heterogeneous functions, slow growth rate, presence of persistent (non-dividing) cells and biofilm phenotype such adaptive mechanisms e.g. efflux pump and membrane which are responsible for conventional antibiotic resistance.7 The biofilm formation itself leads to a resistance to phagocytosis and a reduction in efficacy of anti-microbial agents. Macrolides have been shown to alter the structure and function of biofilm produced by P. aeruginosa, as it was observed that macrolides may be able to reduce tissue damage caused...
Diagnosis

There are a range of signs and symptoms associated with CRS and these symptoms may vary in severity and occurrence. Nasal obstruction (81%-95%) is most common symptom, which is followed by facial congestion-pressure-fullness (70%-85%), discolored nasal discharge (51%-83%) and hyposmia (61%-69%). The presence of 2 or more signs or symptoms continuing beyond 12 weeks is highly sensitive for diagnosing CRS (Table 2).  

Antibiotics in CRS management

While diagnosing CRS, inflammation needs to be documented (polyps, edema, or purulent mucus) in addition to other determined symptoms. An endoscope or a headlight, nasal speculum and an otoscope are usually used for the examination of the nasal cavity. Infrequently, the diagnosis of CRS may be assessed based on objective findings (eg, nasal polyps or CT imaging) when other conditions have been excluded. The diagnostic method, CT scanning is used more often than MRI for diagnosis because of increased cost and hypersensitivity (over diagnosis) of MRI in comparison to CT scanning. 

Treatment options

The major goals of treatment in CRS include eradication of the infection, reduction of sinonasal inflammation, and maintenance of patent sinonasal passage drainage. CRS is generally treated with medical and surgical therapy. Medical therapy usually involves merging multiple medications options including antibiotics, nasal decongestants, topical nasal steroids and/or oral steroids, and saline irrigation (Table 3). Though, some patients do not respond to medical therapy alone; in these cases medical treatment with surgery should be recommended as an alternative. However, surgical interventions are recommended only when there is no response to maximal medical treatment. Management schemes for CRSsNP and CRSwNP are presented in Figure 3.
Macrolide antibiotics are a choice of treatment option for both, CRSsNP and CRSwNP. Macrolide antibiotics have anti-inflammatory and immunomodulatory properties in addition to usual antimicrobial effects, which may be of additional benefit in treating sinonasal disease. Macrolides have generally an acceptable safety profile however health care providers are supposed to refer to the detailed prescribing information for detailed adverse effect profile of individual macrolides. The use of non-macrolide antibiotics for CRS is controversial and its associated potential risks and benefits must be evaluated. Intravenous antibiotics are not usually recommended for routine cases of CRS based on the complications such as thrombophlebitis, neutropenia, venous thromboembolism, rash, and other adverse events. Though, topical antibiotics can deliver high concentrations locally to diseased sinonasal mucosa, are also not recommended for CRS considering their greater extent of side effects compared with a lack of long-term benefit.

Extended spectrum antibiotics (eg, amoxicillin/clavulanic acid, fluoroquinolone) are commonly used. Ciprofloxacin and cefuroxime axetil may be a suitable alternative choice of therapeutic treatment. Short-term antibiotics such as doxycycline reduces polyp size and post-nasal drip score, and other antibiotics such as quinolone, amoxicillin/clavulanate, or co-trimoxazole have shown treatment benefits. Regarding long term antibiotics, the anti-inflammatory effects of macrolides have been evaluated and it shows decrease in polyp size and patient’s symptoms. In addition, the recently published rhinosinusitis practice parameters contain summary statements endorsing the use of antibiotics for CRS (Table 4).

Role of macrolides in CRS treatment

Macrolides belong to the family of 14 or 15 membered lactone ring antibiotics. Macrolides have been found to be beneficial in patients with chronic airway diseases, such as chronic bronchitis, cystic fibrosis, bronchiectasis, bronchial asthma, and CRS. The 14-membered macrolides erythromycin, clarithromycin and roxithromycin and the 15-membered macrolide azithromycin are effective for treating these inflammatory diseases. The mechanism of action of these 14- and 15-membered macrolides may include anti-inflammatory rather than anti-bacterial activities. The guiding principles of macrolide therapy for the treatment of CRS are described in Table 5 and treatment algorithm for macrolides in CRS is described in Figure 4.

Table 4: Recommendations for use of antibiotics in CRS

Antibiotics recommendations (By the Joint Task Force on Practice Parameters)

- Clinicians should use systemic antibiotics for acute exacerbations of CRS.
- Consider a 3- to 6-week course of topical antibiotics for CRS.
- Consider the use of systemic antibiotics plus a short course of oral steroids in the treatment of CRS. Greater benefit with antibiotics has been reported in CRSsNP than in CRSwNP.
- Consider use of antibiotic therapy in acute exacerbations of CRS in children.

(Note: *The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the “Diagnosis and Management of Rhinosinusitis: A Practice Parameter Update”)

Bilateral CRS

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
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<tbody>
<tr>
<td>No Atopy</td>
<td>Atopy Consider other treatment</td>
</tr>
<tr>
<td>Start Roxithromycin 150 mg/d or clarithromycin 250 mg/d</td>
<td></td>
</tr>
<tr>
<td>6 week follow-up (optional)</td>
<td></td>
</tr>
<tr>
<td>12 week follow up, repeat tests and evaluate Clinical response, No side effects</td>
<td></td>
</tr>
<tr>
<td>No effect Consider other treatment</td>
<td></td>
</tr>
<tr>
<td>Stop, wait and see</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Consider continue 6 to 12 months Surgery</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
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</table>

Fig. 4: Treatment algorithm for macrolides in CRS

Table 5: Guiding principles of macrolide therapy for the treatment of CRS

Macrolides used: Erythromycin, Clarithromycin and Roxithromycin

Duration of therapy: Clinical improvement begins 2-4 weeks after the initiation of therapy, and the numbers of patients exhibiting marked improvement continues to increase for 1-3 months. The patients who fail to respond after 3 months of therapy require alternate treatments, such as endoscopic sinus surgery or other drugs.

Relapse of symptoms: Macrolide therapy can be terminated at any time. Some patients experience a relapse after stopping the therapy, but repeated macrolide therapy is also effective in these cases.

Endoscopic sinus surgery: Macrolide therapy is more effective in combination with ESS and nasal irrigation. ESS (ESS) is also effective for treating symptoms remaining after macrolide therapy or symptoms associated with relapse after stopping the therapy.
clarithromycin is commonly used to treat inflammatory diseases and benefits of low-dose, long-term clarithromycin therapy has also been demonstrated for treating CRS.\(^\text{14}\) 

**Mechanisms of action**

**Anti-inflammatory effect**

Macrolides are capable of inhibiting the production of IL-8 by a variety of cell types and may help break the vicious cycle of neutrophil recruitment and further inflammation in chronic airway disease. Moreover, anti-inflammatory cytokines, such as IL-10 and depending on the situation, also IL-1 and IL-6 have been shown to be increased *in vitro* following exposure to macrolides. Nuclear factor-kB (NF-kB) consists of a family of transcription factors that play critical roles in the up-regulation of the inflammatory process. When activity of clarithromycin was evaluated on cultured human nasal epithelial cells and fibroblasts obtained from nasal polyps, it showed that clarithromycin may decrease the expression of IL-1β mRNA through suppression of activation of NF-kB.\(^\text{8}\)

**Effects on mucus production**

In addition to anti-inflammatory effects, macrolides also produce effects on mucous production and mucociliary clearance. The animal study which involved clarithromycin therapy demonstrated that goblet cell hypersecretion in the guinea-pig trachea was reduced by clarithromycin. In patients with CRS treated with clarithromycin, the abnormal viscoelastic properties of their nasal mucus was improved and thus made more suitable for effective mucociliary clearance.\(^\text{8}\)

**Effects on transport of secretion**

Macrolides facilitate transport of secretion. After high dose of clarithromycin (500 mg), almost 30% of increase was found in mucociliary transport. In this study, 18 patients with CRS were managed with clarithromycin 500 mg/d for 4 weeks. The spinability and elasticity was increased and viscosity decreased after administration of clarithromycin. The spinability and percent solid composition of nasal mucus increased from 26.5 ± 12.2 mm to 40.2 ± 18.7 mm and 7.86% ± 3.47% to 13.90% ± 3.67% (p < 0.05), respectively. Thus, the results from this study suggested that treatment with clarithromycin may modulate the rheological properties of nasal mucus in patients with chronic sinusitis.\(^\text{8}\)

- **Dosage of Carithromycin Adults:** Clarithromycin 250 mg or 500 mg every 12 hours for 7–14 days; Clarithromycin 1 gram every 24 hours for 7–14 days.
- **Pediatric patients:** Clarithromycin 15 mg/kg/day divided every 12 hours for 10 days.\(^\text{16}\)

**Clinical evidences**

There are few RCTs that have examined antibiotic use in the CRS patients using placebo arm. Amongst them, five RCTs evaluated long term (three months or more) effect of macrolides. Results were varied and studies including patients with polyps showed some benefit.\(^\text{17}\)

The use of Clarithromycin in CRS had been studied in a few clinical trials. Luo Q et al\(^\text{14}\) evaluated the efficacy of long-term clarithromycin treatment in adult Chinese patients suffering from chronic rhinosinusitis without nasal polyps (CRSsNP). Thirty-three CRSsNP patients received clarithromycin treatment for 12 weeks (250 mg daily). As a controls, 15 patients undergoing transnasal optic decompression because of traumatic neuropathy were enrolled. Clarithromycin therapy significantly improved total nasal symptom scores (TNSS), nasal resistance and Quality of life (QoL), and it inhibited IL-8 and myeloperoxidase (MPO) production in CRSsNP patients (p<0.05) (Figure 5). Thus, the study suggested that long-term, low dose clarithromycin treatment is effective and safe for the treatment of CRSsNP in Chinese patients.

Y fan et al\(^\text{19}\) examined the effect of clarithromycin treatment on T-helper type 2 cytokine IL-5 in nasal secretion to evaluate its immunomodulatory property. Forty-three chronic rhinosinusitis patients were randomised to low-dose or high-dose clarithromycin groups, and their clinical efficacy was evaluated. It was observed that the high dose of clarithromycin was significantly better in terms of clinical efficacy than the low dose for the treatment of CRS (p < 0.025). Significant differences in nasal cytokine levels (IL-5 and IL-8) were also observed between the low-dose and high-dose groups after short-term clarithromycin treatment (p < 0.025) (Figure 6). The study concluded that short-term, high-dose clarithromycin is more effective than low-dose clarithromycin for the treatment of CRS.

Luo Q et al\(^\text{20}\) studied the efficacy of clarithromycin treatment in adult Chinese patients suffering from CRSwNP or CRSsNP. It was a prospective, open and self-controlled clinical trial. The patients received clarithromycin (250 mg/d) for duration of 12 weeks. Significant improvement was observed in symptoms in patients with CRSwNP or CRSsNP. Meanwhile, the efficacy of clarithromycin was found to be more significant in polyp free group compared with polyp group. Also in this study low dose of clarithromycin therapy was found to be tolerable, and the liver function and renal function did not worsen even after 3 months therapy.

Cervin A et al\(^\text{21}\) examined effects of clarithromycin treatment on inflammatory features in CRS. Patients with CRS received treatment with
clarithromycin 250 mg once daily for 12 weeks in an open study design. Clarithromycin reduced the lavage fluid levels of IL-8 at the low-dose histamine observation (P<0.001). There was a trend towards reduced MPO by the treatment, whereas ECP was significantly reduced at the low-dose histamine observation (P=0.05). Clarithromycin also reduces α₂-Macroglobulin (P=0.05). The exudative responsiveness to high dose histamine was significantly reduced by the treatment (P=0.05). The study demonstrated the reduced levels inflammatory products and α₂-macroglobulin (a marker of plasma exudation) following treatment. Thus, long-term treatment with clarithromycin exerts an anti-inflammatory effect in CRS.

Anti-biofilm activity: Clarithromycin vs Azithromycin

Macrolide antibiotics such as erythromycin, clarithromycin, and azithromycin have broad spectrum of activity and anti-biofilm properties. The anti-biofilm activity of clarithromycin was evaluated in vitro with sessile cells of P. aeruginosa. In this study, researchers observed that clarithromycin reduces the amount of alginate and hexaside, both in the colonies and the environment, and thus suggesting destruction of the polysaccharide glycocalyx and/or the inhibition of polysaccharide synthesis. Though, macrolides inhibit biofilm formation in both gram negative and gram positive organisms, clarithromycin is the most widely studied macrolide against mature biofilm of Staphylococcus spp. When the activity of daptomycin and moxifloxacin alone and in combination with clarithromycin against a methicillin-susceptible, clarithromycin-resistant S. aureus strain was evaluated, it was observed that neither daptomycin nor moxifloxacin were able to eradicate mature biofilm, but combination of any of these antimicrobial agents with clarithromycin showed anti-staphylococcal biofilm activity and also significantly improved the antibacterial activity. The activity of azithromycin has also been evaluated against mature Staphylococci biofilms. When the activity of azithromycin combined with daptomycin, vancomycin, tigecycline, fosfomycin or ceftriaxone was assessed on mature biofilms of various non-related strains of S. epidermidis under static conditions of exposure, it was found that none of the combinations were able to produce positive effect on biofilm. Even though there is inadequate data on azithromycin, the absence of anti-biofilm activity of this macrolide against Staphylococci suggests that this may be a specific property of clarithromycin.

Place in the therapy

Chronic rhinosinusitis (CRS) is one of the most common chronic diseases, with very high prevalence. It is usually characterized by persistent inflammation of the sinonasal mucosa. Macrolide antibiotics have anti-inflammatory and immunomodulatory properties, which may be of additional benefit in treating CRS. Macrolides have been shown to accumulate in inflammatory cells at concentrations several hundred-fold higher than concentrations in extracellular fluid. Long-term use of low dosage macrolide antibiotics is recommended for CRS for their anti-inflammatory effects. The present review suggests that clarithromycin can be used as treatment of choice in the management of CRS.

Abbreviations


References