

# Efficacy and Safety of Long-Term Antibiotics (Macrolides) for the Treatment of Chronic Rhinosinusitis

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**Abstract** Long-term treatment of airway inflammation/infection with macrolide antibiotics has now been in use for almost 30 years. Whereas the beneficial clinical effect in cystic fibrosis and COPD have been backed up by randomized controlled trials, the evidence from the upper airways is not as strong. We have identified 22 open studies in chronic rhinosinusitis, with and without polyps, but only 2 randomized controlled trials. Of the controlled trials, the one including CRS patients just without polyps, showed a significant effect in sino-nasal outcome test, saccharine transit time, nasal endoscopy, and IL-8 levels in lavage fluid after 12 weeks of roxithromycin, whereas, in the other RCT with a mixed study group of CRS patients with and without polyps, 12 weeks of azithromycin showed no effect compared to placebo. Concerns regarding the risk of macrolides to induce arrhythmia have been raised. Recent FDA guidelines changes has recommended caution in patients with risk factors such as long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia. Ototoxicity is another concern. Long-term macrolide antibiotics in the treatment of CRS patients is still a viable option in a select group of patients.

**Keywords** Antibiotics · Efficacy · Chronic rhinosinusitis · Airway · Chronic sinusitis · Nasal polyp · Macrolide · Azithromycin · Erythromycin · Clarithromycin · Roxithromycin · Clinical trials · Outcome · Mortality · Safety · Adverse effects · Interaction · QT syndrome · Resistance · Treatment

## Introduction

Erythromycin was discovered in a soil sample from the Philippines in the mid-1950s. It was the first substance in a new class of antibiotics called macrolides. Since then, synthetic variations have led to macrolide compounds with better absorption from the gut and with longer half-life. A chemical related to macrolides is the immunosuppressant Tacrolimus, or Fujimycin, also found in a soil sample in 1984, but this time in Japan. There are a number of antibiotic macrolides available. The most commonly used, and having FDA approval, are, erythromycin, clarithromycin, roxithromycin, and azithromycin, the latter unique among macrolides by not inhibiting CYP3A4. It is also called cytochrome p450, involved in drug metabolism and the synthesis of cholesterol and steroids.

Macrolides were originally used to treat infections by Gram-positive bacteria. However, in 1984, Kudoh reported the successful treatment of diffuse panbronchiolitis, changing the 5-year survival rate from approximately 25 to 90 % [1]. Since then, macrolides have been trialed in a number of inflammatory conditions including, foremost, the airways, but even targeting arteriosclerosis.

There is a wealth of in vitro studies available demonstrating macrolides' immune modulatory and anti-inflammatory effects. Effects include the reduction of pro-inflammatory cytokines such as IL-5, IL-6 and IL-8, inhibition of oxidative burst

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**Table 1** Level of evidence-recommendations-relevance in the long-term (>4 weeks) use of macrolide antibiotics in chronic rhinosinusitis

| Phenotype           | Evidence            | Recommendation                                                       | Relevance                |
|---------------------|---------------------|----------------------------------------------------------------------|--------------------------|
| CRSwNP              | 2b                  | C (non-randomized cohort studies, efficacy less well established)    | Yes                      |
| CRSSNP              | 1b pos <sup>a</sup> | A (One randomized placebo controlled trial)                          | Yes, if IgE not elevated |
| Mixed CRSwNP/CRSSNP | 1b neg <sup>b</sup> | C (contradictory studies, both randomized placebo-controlled trials) | Yes                      |
| Preop treatment     | 2a                  | B (non-randomized cohort studies in favor of treatment)              | Yes                      |
| Postop treatment    | 2a                  | B (non-randomized cohort studies in favor of treatment)              | Yes                      |

<sup>a</sup> Wallwork et al. [11]<sup>b</sup> Videler et al. [26••]

and degranulation of neutrophils, and stimulation of phagocytosis, to name just a few [2–9].

However, it has been difficult to confirm these mechanisms in a clinical setting, although a reduction of IL-6 and IL-8 in nasal lavage after macrolide treatment has been observed [10, 11].

In this review, we will look at the recent developments concerning clinical efficacy of macrolide antibiotics in the treatment of chronic rhinosinusitis and take a closer look at the recent reports on cardiovascular deaths possibly related to macrolide use.

## Search Strategy

Pubmed, EMBASE, Summon, Controlled trials, Registry of the Cochrane library, and Google Scholar were searched. The search strategy was wide and included: chronic sinusitis, rhinosinusitis, nasal polyp, macrolide (including azithromycin, erythromycin, clarithromycin, roxithromycin), clinical trials, outcome, mortality, safety, adverse effects, QT syndrome, and resistance. We have emphasized the more recent studies and, in non-randomized trials, have focused on hard data such as laboratory findings. Case reports and studies published in languages other than English have been excluded. The search was performed in November 2013.

## Early cohort reports

We have identified 22 publications in total presenting long-term (in this context defined as 4 weeks or more) use of macrolide antibiotics, in the treatment of chronic rhinosinusitis (CRS) with (CRSwNP) or without (CRSSNP) nasal polyps. However, only 2 studies had a placebo arm.

We will first briefly discuss the non-randomized trials before 2010. They have all shown favorable results concerning the reduction of symptoms such as post-nasal drip, nasal congestion, and headaches. Of interest are the studies that have tried to objectively measure inflammatory parameters. In a study by Haruna et al. from 2009, it was concluded from treating 68 adults for 8–20 weeks that the poor responders were found in the group

with nasal polyps and that the relationship of eosinophils compared to total inflammatory cells in nasal polyps were especially high in the non-responding group. Also, the group with bronchial asthma had fewer responders [12]. A previous Japanese study analyzed eosinophil count in peripheral blood, nasal smear, and in-sinus mucosa together with serum IgE. They found an inverse correlation between eosinophil count and symptomatic improvement. The higher the eosinophil count, the poorer the result. They also showed that the patients with normal IgE levels were significantly more likely to respond to the macrolide treatment [13]. The findings regarding normal IgE levels and a higher likelihood of a favorable outcome were later replicated by Wallwork et al. in a placebo-controlled trial [11]. A study by Yamada et al. analyzed IL-8 in nasal lavage in CRSwNP. Patients were treated with macrolides for a minimum of 3 months. The best outcome was seen in the group with high IL-8 levels, in which polyp size was dramatically reduced. Comparing the non-responders with responders, the IL-8 levels in nasal lavage were significantly ( $p<0.005$ ) higher in the responding group [10].

A prospective study compared endoscopic sinus surgery with 12 weeks of macrolide antibiotic treatment in 90 patients, which revealed significant improvements in both groups. Monitored parameters included SNOT-20, SF-36, and saccharine transit time. The only difference was noted in nasal volume where surgery was more effective [14].

## Recent cohort reports

The last 3 years have seen no less than 5 uncontrolled trials coming out of China, of which 3 have been published in English. One compared mometasone furoate 200 mg with clarithromycin 250 mg once a day for 12 weeks. There were 21 and 22 patients in each group, respectively. After 4 weeks, there were already significant reductions of total nasal symptom score as well as nasal obstruction, headaches, and rhinorrhea in both groups. There were no significant differences between the mometasone furoate or clarithromycin group except that, in the group with allergic co-morbidity, the nasal steroid spray was correlated with lower scores in oedema and secretions [15]. One has to bear in mind that the

Chinese population has a more neutrophilic nasal polyp disease than the western population, which may lend itself better to macrolide treatment [16].

Another Chinese study published in English compared the efficacy of traditional herbal medicine ( $n=26$ ) against erythromycin ( $n=27$ ) for 8 weeks in a cohort of patients with CRSsNP. SNOT-20, endoscopy, and saccharine transit time was used for evaluation, and it was concluded that the effect was similar in both groups regarding SNOT-20, which was significantly improved. Saccharine transit time was shorter in the herbal group compared to the macrolide group [17].

A third study from China treated 33 patients with CRSsNP with 250 mg of clarithromycin daily for 12 weeks. Evaluation included total nasal symptom score (TNSS), nasal resistance, IL-8, and MPO. Clarithromycin significantly improved all parameters. One interesting objective finding was that the group with high IL-8 responded significantly ( $p<0.05$ ) better than the group with low IL-8, replicating previous studies cited above [18].

While drawing conclusions from the uncontrolled trials must be done with caution, it seems that there are subgroups of CRS patients that are more likely to respond to macrolide treatment (high IL-8 in nasal secretions or normal serum IgE), highlighting the need to phenotype our patients before considering macrolide treatment and not accepting CRS alone as a diagnosis.

A Japanese multicenter study enrolled 424 subjects with chronic rhinosinusitis without polyps or small polyps, defined as a polyp score of 0 or 1 according to Tos. The study was prospective and randomized but open label. It compared clarithromycin (200 mg/day) versus a combination of clarithromycin and the mucolytic S-carboxymethylcysteine (1,500 mg/day). Both groups were treated for 12 weeks, and 159 and 158 patients were evaluated, respectively, with 54 patients in each group being excluded due to violation of study protocol. SNOT score was evaluated at 4, 8, and 12 weeks, and showed progressive significant improvement from week 4 onwards. There were no differences between the groups. There was also a significant reduction in CT score at week 12 compared to inclusion. Raised liver function test were found in 6 patients during the course of the trial [19].

Videler has retrospectively compared the outcome of long-term macrolide treatment with long-term trimethoprim-sulfamethoxazole treatment in a mixed cohort of difficult-to-treat CRS patients,  $n=76$ . Seventy-eight percent of the patients responded to treatment according to a 5-point grading scale of sinus complaints and there was no difference between the groups [20].

### The role of treatment duration

Another recent study from Japan investigated the possible differences of postoperative use of clarithromycin (200 mg/

day) for 3 or 6 months. All patients improved, however, at 12 months follow-up, the 6 months treated group had a significantly better VAS score for post-nasal drip and rhinorrhea.

The role of treatment length has been analyzed in several studies. Although one has to be wary of the fact that placebo control groups are missing and that perhaps it reflects the natural course, the results suggest that the longer one treats patients the greater reduction in symptom scoring [21]. Cervin et al. showed a further significant reduction of symptoms and improvement in saccharine transit time, at 12 months compared to 3 months [22]. Hashiba showed that improvement rate went up as the treatment progressed. Comparing 2, 4, 8, and 12 weeks, improvement rate went from 4.7 to 47.7 to 62.8 to 70.6 % [23]. It is speculated that restoration of mucosa is slow and needs more than 12 weeks to regenerate a normal mucosa where hyperplasia and goblet cell proliferation has been reduced. A second reason could be reduced risk of re-infection while on macrolide treatment.

### Cohort studies in CRSwNP

Two recent open studies, which investigate the effect of macrolides on nasal polyp patients have recently been published.

An interesting study from Serbia and Norway investigated the effect of clarithromycin 500 mg/day for 8 weeks on nasal secretions of RANTES, IL-4, -5, -6, and eosinophilic cationic protein. Of 40 patients with CRSwNP, 22 were non-allergic and 18 has allergic co-morbidity. Responders were 69 % in the non-allergic group and 56 % in the allergic group. All patients had remaining polyps but there was a significant reduction in polyp score in both the allergic and non-allergic patients. RANTES was significantly decreased in both groups in nasal secretions, whereas in the non-allergic groups, ECP was significantly reduced, and in the allergic group, IL-6 was reduced. The authors speculate that clarithromycin works through suppression of nasal fibroblast proliferation, and that clarithromycin seems to have different immune modulatory effects depending on the presence of allergies [24].

Another study by Dabirmoghaddam focusing on nasal polyp patients has recently been published. Of 43 patients who were enrolled, 3 were lost to follow-up, 8 were smokers, 5 had asthma, and 2 had NSAID intolerance. VAS scales were used before and after treatment. Clarithromycin was used in a rather high dose of 500 mg twice a day for 8 weeks. There was a significant improvement in sense of smell, rhinorrhea, and nasal obstruction. Lund Mackay score changed from 20.4 to 14.2, ( $p<0.001$ ). There were 29 patients with a decrease in polyp size and 11 without any improvement, a 72 % response rate. A total of 23 patients were available for a 3-month follow-up after cessation of therapy, of whom 2 showed polyp regrowth and the others remained stable. The author

concluded that, although there was a reduction of polyp size, no patient went into complete remission [25].

### Randomised placebo controlled trials

Two placebo-controlled studies have been published over the last 10 years. The first by Wallwork et al. targeted CRSsNP patients and included 64 patients divided in to two groups, either receiving placebo or roxithromycin 150 mg daily. Statistically significant improvements were seen in SNOT-20, saccharine transit time and nasal endoscopy. It was noted that there were more responders in the normal serum IgE group compared to high IgE group. The overall response rate was 67 % in the treatment group versus 22 % in the placebo group. The study was performed in a single center [11]. A more recent multicenter study by Videler and co-workers, included 60 patients randomized to azithromycin or placebo. Patients were given placebo or azithromycin 500 mg for 3 days during the first week followed by 500 mg per week for the next 11 weeks. Assessment included SNOT-22, SF-36, VAS, patient response rating scale, peak nasal inspiratory flow and nasal endoscopy. Overall response rate in the treatment group was 44 % compared to 28 % in the placebo group, which did not reach significance [26••]. A possible explanation for the lack of effect can be attributed to the inclusion criteria whereas the Videler study included patients both with and without polyps, furthermore requiring a minimum CT score according to Mackay-Lund of at least 5, suggesting a more hyperplastic rhinosinusitis. Although there were no records of serum IgE, it is not unlikely that the cohort studied contained a larger proportion of patients with elevated IgE, reducing the numbers of likely responders.

### Summing up the present knowledge on effect

The EPOS 2012 document concluded that the level of evidence for macrolide treatment in CRSsNP is 1b, strength of recommendation is C, due to the two contradictory studies cited above. However, if patients are phenotyped with serum IgE and are found to have normal IgE levels, the recommendation is A [27••]. (Table 1).

If one is disappointed with the conflicting evidence for long-term, low-dose macrolide treatment in CRS, one has to bear in mind that other antibiotics, such as tetracyclines and trimethoprim-sulfamethoxazole, which have shown some promise in retrospective studies, have been studied even less.

Large randomized controlled studies with a well-defined study population are long overdue in CRS. The present investigations lack the high power seen in studies from the lower airways. One example is a recent study on COPD and azithromycin which included 1,577 patients. It showed a

significant effect on exacerbation rate and health where previous smaller studies,  $n < 100$ , have been inconclusive [28]. Furthermore, limited data suggest it is time to investigate the role of other non-penicillin antibiotics such as tetracycline and trimethoprim-sulfamethoxazole as treatment options in CRS [20•].

### Macrolide interactions

Many drugs undergo biotransformation via the hepatic or intestinal cytochrome P-450 system, also known as the mixed-function oxidase system. Three families of cytochromes perform this oxidative function in humans and there a number of isoforms of each [29]. Macrolides are transformed in the liver to nitrosalkanes which can subsequently form inactive complexes with the CYP 3A4 isoform, resulting in inhibition of CYP 3A4-mediated activity [30]. This mechanism accounts for the majority of macrolide drug interactions.

Different macrolides have differing abilities to bind and inhibit the cytochrome P-450 system [30]. In addition, individual patients have differing intrinsic cytochrome P-450 activity due to genetic factors, dietary factors, and illness. This interindividual variability provides some explanation as to why some patients are more prone to drug interactions with macrolides.

The following drugs have a well-documented interaction with macrolides.

**Warfarin** The R-warfarin form of warfarin in particular is metabolized by the CYP 3A4 isoform. Erythromycin in particular has been reported to increase the hypothermbinaemic effect of warfarin and to decrease warfarin clearance by 14 % in healthy volunteers [31]. This effect is thought to be potentiated by other factors such as the disease state. The semi-synthetic macrolides (azithromycin and clarithromycin) are thought to interact less with warfarin, but careful monitoring of coagulation profile is recommended in patients undergoing concomitant treatment [29].

**Cisapride** Cisapride is associated with the formation of cardiac dysrhythmias. More than half of the reported cases of cardiac dysrhythmias, prolonged QT intervals, and death due to cisapride are due to interactions with drugs known to inhibit CYP3A4, such as macrolides [32].

**Psychotropic drugs** Coadministration of macrolides with benzodiazepines can lead to increased oral bioavailability and elimination half-life and should therefore be avoided or the dose of benzodiazepine should be reduced [33]. Similarly, increased side effects of the atypical antipsychotic agent

clozapine have been described with erythromycin administration [34].

**Cyclosporin** The immunosuppressive agent cyclosporin is extensively metabolized by the CYP3A4 pathway and can cause concentration-related renal toxicity. There are several reports of reduced clearance of cyclosporine with macrolide administration, and therefore cyclosporine levels and renal function should be monitored closely when they are administered together [35].

**Non-sedating antihistamines** Some non-sedating antihistamines such as terfenadine can lead to prolongation of the QT interval, and this risk is increased with macrolide administration [36]. A study of clarithromycin and loratadine coadministration showed increased concentrations of loratadine and its active metabolite but no ECG changes were observed. It was concluded that loratadine has a wide margin of safety and that the observed interaction was probably not important [37].

**HMG-CoA reductase inhibitors or statins** Coprescription of a statin (used for lowering cholesterol) and some macrolides has been shown to increase statin toxicity. A 2013 study from Ontario, Canada, reported an increased risk of hospitalization for rhabdomyolysis, acute renal injury, and all-cause mortality when statins were prescribed with clarithromycin or erythromycin compared to azithromycin, which does not utilize the cytochrome P450 3A4 isoenzyme [38].

Other known interactions with macrolides include theophylline, carbamazepine, and quinidine [29].

## Macrolide side effects

**Cardiovascular side effects** Macrolide administration can result in prolongation of the QT interval and the subsequent arrhythmia torsades de pointes. Ray et al., [39] in an observational study reported the risk of death due to all causes and cardiovascular death specifically was increased with azithromycin use compared to amoxicillin use or no antibiotic use. The risk varied with the presence or absence of cardiovascular risk factors. It was estimated that there was one excess cardiovascular death per 4,100 prescriptions among patients at high cardiovascular risk but less than 1 per 100,000 among patients with lower cardiovascular risk. The American Food and Drug Administration has now changed labeling of azithromycin to advise against use in patients with risk factors such as QT-interval prolongation, hypokalemia, hypomagnesemia, bradycardia, or those using certain antiarrhythmic agents that can prolong the QT interval, including class IA (e.g., quinidine and procainamide) and class III (e.g.,

dofetilide, amiodarone, and sotalol) [40]. In a prospective analysis of almost 3,000 patients in the United Kingdom with acute exacerbations of COPD or with community-acquired pneumonia, treatment with clarithromycin was associated with a significantly increased risk of acute cardiovascular events, with a hazard ratio of 1.50 to 1.68. Longer courses of clarithromycin, more than 7 days, were associated with a greater risk, especially with a pre-existing condition of coronary heart disease. No increased risk was seen with Doxycycline or beta-lactam antibiotics [41••].

**Gastrointestinal side effects** With macrolides are by far the most common adverse reaction and are thought to be due to increased gut motility. Symptoms include abdominal pain, diarrhea, nausea, and vomiting. These effects are seen in 15–20 % of patients receiving erythromycin but in less than 5 % in patients receiving the newer synthetic macrolides [42].

**Hearing loss** Sensorineural hearing loss may occur secondary to macrolide administration. Most frequently, this is seen in patients receiving high doses or those with impaired hepatic/renal function. The hearing loss is generally transient. Toxicity is more likely to be ototoxic than vestibulotoxic. In a recent study of 1,577 COPD patients receiving azithromycin for 12 months, 27 % of patients receiving the macrolide had a hearing deterioration compared to 21 % receiving placebo. There was a significant deterioration in hearing thresholds in the macrolide group [28].

**Other side effects** Allergic reaction to macrolides are uncommon and are estimated to occur in approximately 0.5 % of cases. The most common manifestation is rash [42]. Hepatotoxicity due to cholestatic hepatitis has also rarely been reported.

## Conclusions

The anti-inflammatory action of macrolide antibiotics has been demonstrated both in vitro as well as in vivo, although the mode of action in vivo is not clear.

The risk of arrhythmia has to be considered as low in the population without risk factors. However, vigilance is needed in checking for interactions with warfarin, antihistamines, anti-arrhythmic agents and statins as well as a history of heart disease.

Considering that the present treatment strategies in CRS, based on steroids, nasal saline lavage, short-term antibiotics, and surgery fails to provide symptom control in up to a third of CRS patients, other treatment modalities are needed. The authors believe that there is support for macrolide treatment of chronic rhinosinusitis in patients in absence of high IgE

levels, where standard treatment has failed and caution has been taken to identify risk factors for interaction and cardiovascular events. However, with the recent evidence of cardiovascular risk, it is even more urgent to properly investigate the role of other antibiotics in the treatment of CRS.

It is time for a large randomized controlled trial in a well-phenotyped CRS population to evaluate the role of macrolide antibiotics, as well as tetracyclines and trimethoprim-sulfamethoxazole, in upper airway inflammation/infection.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Anders Cervin and Ben Wallwork declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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