

Introducing a Novel Combination Therapy with Macrolides for the Treatment of Chronic Rhinosinusitis: A Randomized Controlled Trial

Mehdi Askari¹, MD;  Mehrdad Khezri², MD; Ghazal Zoghi³, MD

¹Department of Otorhinolaryngology, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran;

²Department of Radiology, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran;

³Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

Correspondence:

Mehdi Askari, MD;

School of Medicine, Across from Kargaran Sports Complex, Imam Hossein Blvd., Postal code: 79196-93116, Bandar Abbas, Iran

Tel: +98 76 33710370

Fax: +98 76 33710371

Email: mehdi.askar913@gmail.com

Received: 07 July 2021

Revised: 25 October 2021

Accepted: 21 November 2021

What's Known

- Macrolides have shown beneficial effects in treating chronic rhinosinusitis (CRS).
- The use of macrolides in the treatment of CRS mainly relies on their anti-inflammatory properties rather than their antimicrobial effect.

What's New

- In combination with conventional therapies for CRS in adults, a four-week course of azithromycin is more effective than clarithromycin.
- Nonspecific anti-inflammatory agents together with decongestants, nasal irrigation, and steam inhalation may increase the efficacy of macrolides in the treatment of CRS.

Abstract

Background: Macrolides have shown beneficial effects in the treatment of chronic rhinosinusitis (CRS). This study aimed to compare the effect of azithromycin and clarithromycin in combination with conventional therapies for the treatment of CRS.

Methods: This single-blind randomized controlled trial was conducted during 2018-2019 at the Otorhinolaryngology Clinic of Shahid Mohammadi Hospital, Bandar Abbas, Iran. Out of 102 selected patients, 90 were included in the analysis. Patients were selected through convenience sampling and randomly assigned to two equal groups. In addition to conventional therapies (nasal irrigation, betamethasone injection, oxymetazoline and fluticasone spray, guaifenesin syrup, and steam inhalation), the patients in the clarithromycin group received clarithromycin 500 mg tablets twice daily for four weeks. The other group received azithromycin 500 mg tablets daily for four weeks. Patients' symptoms were evaluated pre- and post-intervention, and the Lund-Mackay (LM) scoring system was used for the staging of CRS based on computed tomography scan findings. Data were analyzed using SPSS software, and $P < 0.05$ was considered statistically significant.

Results: Patients in both groups were comparable in terms of age and sex. Complete resolution of symptoms was significantly higher in the azithromycin group than the clarithromycin group (71.1% vs. 24.4%, $P < 0.001$). Baseline LM scores did not differ significantly between the groups ($P = 0.120$). However, post-intervention, LM scores reduced considerably in both groups, but the change was significantly higher in the azithromycin group ($P < 0.001$).

Conclusion: In combination with conventional therapies for CRS in adults, a four-week course of treatment with azithromycin is more effective than clarithromycin.

Trial Registration Number: IRCT20201209049661N1.

Please cite this article as: Askari M, Khezri M, Zoghi G. Introducing a Novel Combination Therapy with Macrolides for the Treatment of Chronic Rhinosinusitis: A Randomized Controlled Trial. Iran J Med Sci. 2022;47(6):533-540. doi: 10.30476/IJMS.2021.91813.2303.

Keywords • Azithromycin • Chronic sinusitis • Clarithromycin • Drug therapy • Combination • Macrolides

Introduction

Chronic rhinosinusitis (CRS) is defined as the inflammation of paranasal sinuses lasting for at least 12 consecutive weeks.¹ Considering the inflammatory nature of the disease, the role of

antibiotics in the treatment of CRS is not clear, and there is limited evidence to support their effectiveness.² Given that the contribution of microbes to the pathogenesis of CRS is debatable, and CRS is not primarily an infectious process, it appears that bacteria are generally present in CRS and play an important role in the severity and persistence of the disease.³ Despite the lack of sufficient data on the efficacy of oral antibiotics, they are frequently prescribed for CRS. A few studies investigated the effect of antibiotics on CRS, such as doxycycline, erythromycin, clarithromycin, roxithromycin, and azithromycin.⁴⁻⁸ It was reported that doxycycline was more effective in CRS patients with nasal polyps.⁵ Among the available antibiotics, macrolides have shown acceptable bioavailability and tissue penetration when administered orally.⁶ In addition to antimicrobial effects, this class of antibiotics has immunomodulatory and anti-inflammatory properties.⁷ In fact, the rationale for the use of macrolides in the treatment of CRS mainly relies on their anti-inflammatory properties rather than their antimicrobial effect.⁸

Macrolides have excellent sinus tissue penetration, which is partly due to their large volume of distribution by leukocyte migration to the site of inflammation or infection. The second-generation macrolides derived from erythromycin are clarithromycin and azithromycin. The half-life of clarithromycin allows sustained concentration in the sinus fluid with once-daily dosing, whereas azithromycin has a much longer half-life allowing sustained concentration for up to 120 hours.⁹ However, Margaritis and colleagues found that clarithromycin concentration in the sinus fluid was significantly higher than azithromycin at two, six, and 12 hours after administration.¹⁰ Overall, there are conflicting reports on the efficacy of these macrolides for the treatment of CRS. In a randomized clinical trial, the beneficial effect of clarithromycin was reported.¹¹ However, another study found no therapeutic benefit from the concomitant use of clarithromycin and mometasone furoate nasal spray.¹² As for azithromycin, treatment of CRS patients for three months did not show a significant benefit compared to placebo.¹³ Nonetheless, azithromycin in combination with conventional therapy is shown to significantly reduce the recurrence rate of CRS after functional endoscopic sinus surgery.¹⁴

To the best of our knowledge, no previous study has compared the efficacy of clarithromycin and azithromycin in the treatment of CRS. Considering the potential of macrolides in the treatment of CRS, there have been only limited studies on their effectiveness, especially of azithromycin. The present study aimed

to compare the effect of clarithromycin and azithromycin in combination with conventional therapies for the treatment of CRS.

Patients and Methods

This single-blind randomized controlled trial was conducted during 2018-2019 at the Otorhinolaryngology Clinic of Shahid Mohammadi Hospital, Bandar Abbas, Iran. The target population was patients aged 18-65 years, diagnosed with CRS in accordance with the American Academy of Otolaryngology-Head and Neck Surgery Rhinosinusitis Task Force (RTF) guideline,¹⁵ and confirmed CRS with computed tomography (CT) scan. Exclusion criteria were the presence of a polyp, mass, or severe nasal septal deviation (requiring surgery or obstructing the sinus ostia) upon endoscopic examination, use of antibiotics within the prior six weeks, history of topical corticosteroid administration within the prior month, sinus or nasal surgery, hypersensitivity to macrolides, pregnancy or lactation, diabetes mellitus, hypertension, cardiovascular diseases, periodontal infection of the tooth roots adjacent to the maxillary sinus; and systemic illnesses involving the sinuses including Wegener's granulomatosis, sarcoidosis, malignancies, lymphoma, cystic fibrosis, acquired immunodeficiency syndrome, primary ciliary dyskinesia, and the like. Excluded were also those patients with CT scan findings of inhomogeneous densities indicating probable fungal infections, unilateral involvement of the maxillary sinuses, and presence of mucous retention cysts in the maxillary sinus. Periodontal infections had to be ruled out if reactive changes of the sinus floor were observed in the CT scan.

The sample size of at least 40 was calculated based on $\alpha=0.05$, $\beta=0.1$, $d=2.8$, and $P=0.5$. The results of a pilot study using the Lund-Mackay (LM) score system before and after intervention in the σ_1 group were determined as 5.5 and 3.6, and in the σ_2 group as 3.9 and 5.1. The following formula was used for sample size calculation.¹⁶

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 (S_{change\ 1}^2 - S_{change\ 2}^2)^2}{d^2}$$

$$S_{change\ 1}^2 = \sigma_{before\ 1}^2 + \sigma_{after\ 1}^2 - 2P \times \sigma_{before\ 1}^2 \times \sigma_{after\ 1}^2$$

$$S_{change\ 2}^2 = \sigma_{before\ 2}^2 + \sigma_{after\ 2}^2 - 2P \times \sigma_{before\ 2}^2 \times \sigma_{after\ 2}^2$$

$$z_{1-\alpha/2} = 1.96$$

$$Z_{1-\beta} = 0.84$$

$$\sigma_{before\ 1} = 5.5$$

$$\sigma_{after\ 1} = 3.6$$

$$\sigma_{before\ 2} = 3.9$$

$$\sigma_{after\ 2} = 5.1$$

$$d = 2.8$$

$$P = 0.5$$

After initial assessments, all patients underwent anterior rhinoscopy by an experienced otorhinolaryngologist using a standard nasal speculum. A cotton ball moistened with 0.5% phenylephrine nasal drop (Ramopharmin Pharmaceutical Co., Iran) and 0.5% tetracaine hydrochloride solution (Daroupakhsh Pharmaceutical Co., Iran) was placed in the patient's nostrils and left for 15 min. Then, nasal endoscopy was performed using a 30-degree-lens endoscope. Besides, a non-contrast CT scan of the paranasal sinuses was performed with 5 mm coronal cross-sections. Subsequently, using the convenience sampling method, 102 patients who met the inclusion criteria entered the study. Based on the simple randomization method, the patients were assigned to two groups, namely the clarithromycin (n=53) and azithromycin (n=49) groups. A randomization table was generated using the Random Allocation software, version 1.0 (developed by M. Saghaei MD, Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran). Sealed envelopes, each containing the name of a participant, were used by the physician in charge of the study to allocate patients to each group. The patients in the clarithromycin group received clarithromycin 500 mg tablets (Tehran Chemie Pharmaceutical Co., Iran) twice daily for four weeks. The other group received azithromycin 500 mg tablets (SANA MED Pharmaceutical Co., Iran) daily for four weeks. The researcher, who evaluated the patients, was blinded to the groups.

All participants received the following treatments:

1. Bilateral nasal irrigation with 20 mL normal saline using a 20-gauge syringe four times a day followed by two puffs of oxymetazoline 0.1% nasal spray (Jaber Ebne Hayyan Pharmaceutical Co., Iran) in each nostril four times a day for five days.

2. Two puffs of fluticasone propionate nasal spray (50 mcg/dose FLUNIX, Jaber Ebne Hayyan Pharmaceutical Co., Iran) in each nostril four times a day for two weeks and then twice a day for two weeks followed by steam inhalation for 10 min for a week.

3. Two intramuscular injections of long-acting betamethasone (Caspian Tamin Pharmaceutical Co. Iran) two weeks apart, 5 mL guaifenesin syrup (100 mg in 5 mL; Ramopharmin Pharmaceutical Co., Iran) three times a day for 10 days, and fexofenadine hydrochloride 120 mg film-coated tablets (Telfast, Sanofi, UK) once a day at bedtime in case of allergic symptoms including rhinorrhea and nasal itching.

The LM score system was used for the staging of CRS based on the CT scan findings. The score ranges from 0 to 24, where 0

indicates complete lucency of all sinuses and 24 complete opacity of all sinuses.¹⁷ In this system, right- and left-sided sinuses are evaluated separately. Each side includes six structures, namely maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinuses as well as the ostiomeatal complex (OMC). A score of 0, 1, or 2 is allocated to each sinus, where 0 indicates complete lucency, 1 partial lucency/opacity, and 2 complete opacity. Note that a score of 0 is allocated to mucosal thickening lower than 1-2 mm without fluid accumulation. In addition, the OMC is assigned a score of either 0 (not obstructed) or 2 (obstructed). The primary outcome was defined as resolution of CRS symptoms and reduction in the LM score.

The study was approved by the Institutional Review Board of Hormozgan University of Medical Sciences, Bandar Abbas, Iran (code: HUMS.REC.1395.76). The study was registered in the Iranian Registry of Clinical Trials (IRCT20201209049661N1) available at <https://www.irct.ir/trial/53511>. Written informed consent was obtained from all the participants.

Statistical Analysis

Data were analyzed using SPSS software, version 25.0 (Armonk, NY: IBM Corp., US) and expressed as mean, median, standard deviation, interquartile range (IQR), frequency, and percentages. Kolmogorov-Smirnov test was used to examine the normal distribution of quantitative variables. An independent *t* test was used to determine age differences between the two groups. Mann-Whitney and Wilcoxon tests were used to compare pre- and post-intervention LM scores between and within groups, respectively. Chi squared and Fisher's exact tests were used to compare the frequencies between the groups. P values less than 0.05 were considered statistically significant.

Results

Of the 102 CRS patients, four patients in the azithromycin group and eight in the clarithromycin group discontinued intervention due to acute gastrointestinal symptoms and were thus excluded from the final analysis (figure 1). The mean age of the remaining 90 patients was 31.24±12.21 (18-65) years, out of which 40 (44.4%) were male and 50 (55.6%) were female patients. The mean age of patients in the azithromycin (n=45) and clarithromycin (n=45) groups was 30.62±11.73 and 31.87±12.77 years, respectively (P=0.631). The sex distribution of patients in each group was similar; 20 (44.4%) were male patients, and 25 (55.6%) were female patients.

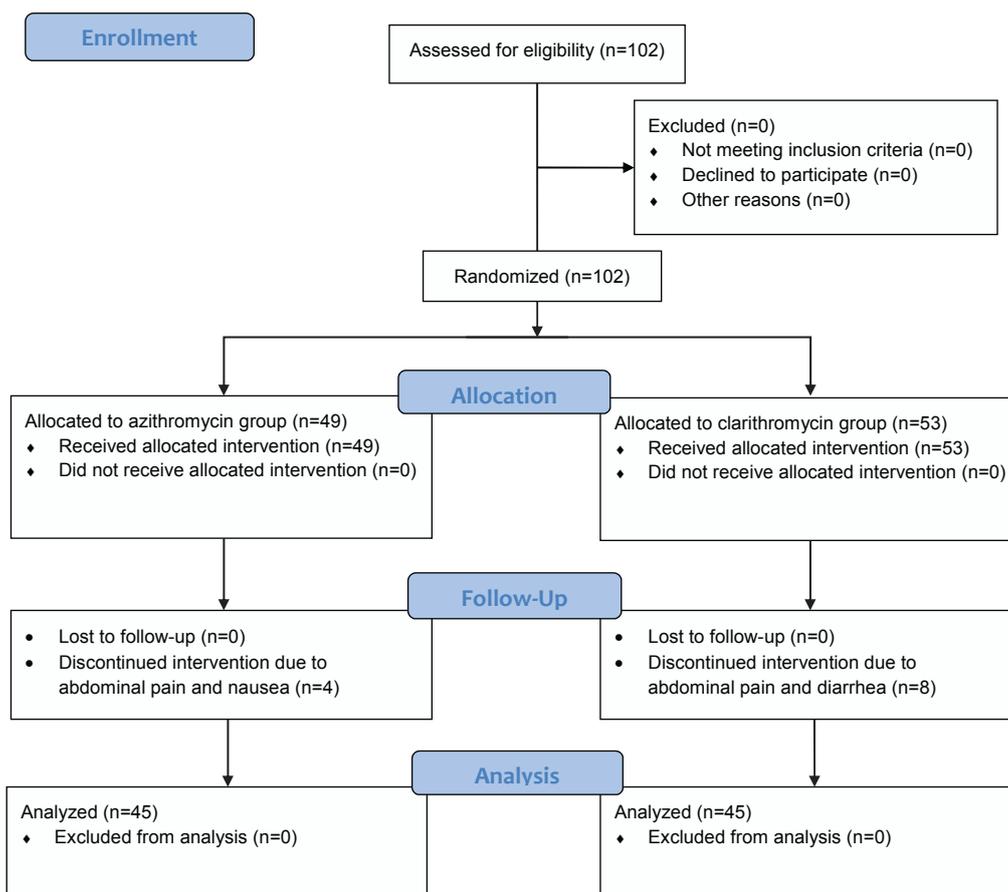


Figure 1: The figure represents the CONSORT flow diagram of the study.

The CT scan findings did not show a significant difference in pre-intervention LM scores between the groups (P=0.120). However, post-intervention, LM scores in the azithromycin group were significantly lower than in the clarithromycin group (1 [IQR: 0-2] vs. 5 [IQR: 2-10], P<0.001). Although post-intervention LM scores decreased significantly in both groups (P<0.001), the change was significantly higher in the azithromycin group (table 1).

In terms of treatment outcome, complete resolution of symptoms was observed in 71.1%

(32/45) of the azithromycin group and 24.4% (11/45) of the clarithromycin group. Partial resolution of the symptoms was higher in the clarithromycin group, while in 4/45 (8.9%) of the azithromycin group there was no change in clinical symptoms, which was much lower than the 42.2% in the clarithromycin group (P<0.001) (table 2).

Discussion

The results of the present study showed that

Table 1: Comparison of pre- and post-intervention LM scores between and within the azithromycin and clarithromycin groups

LM scores	Azithromycin (median, IQR)	Clarithromycin (median, IQR)	P value*
Pre-intervention	16 (12-24)	14 (10.5-18)	0.120
Post-intervention	1 (0-2)	5 (2-10)	<0.001
Change	14 (11-19)	8 (7-9.5)	<0.001
P value†	<0.001	<0.001	-

IQR: Interquartile range; LM: Lund-Mackay; *Mann-Whitney test (between groups); †Wilcoxon test (pre- and post-intervention within groups)

Table 2: Comparison of symptom resolution between the azithromycin and clarithromycin groups

Symptoms	Azithromycin	Clarithromycin	P value*
Complete resolution	32 (71.1)	11 (24.4)	<0.001
Partial resolution	9 (20)	15 (33.3)	
No change	4 (8.9)	19 (42.2)	

Data are expressed as numbers and percentages. *Chi square test

for CRS in adults, a four-week combination of conventional therapies and azithromycin 500 mg daily was more effective than clarithromycin 1,000 mg daily. To date, no other study has compared the efficacy of these two macrolides in the treatment of CRS. Besides, a literature review revealed inconsistent findings on the effect of macrolides. A recent meta-analysis of 10 studies showed no difference in the Sino-Nasal Outcome Test (SNOT), symptom score, and endoscopy score between standard treatment in combination with and without macrolides.⁸ In line with our findings, in a subgroup analysis in which patients with nasal polyps were excluded, macrolides were shown to be more effective than placebo.¹⁸ A meta-analysis consisting of 17 randomized clinical trials demonstrated that adding oral clarithromycin to nasal corticosteroids improved clinical symptoms of CRS patients in both medium- and long-term (1-3 months and >3 months, respectively). The LM score was also improved in the short term with this combination therapy (<1 month). However, symptoms and LM scores did not improve significantly with clarithromycin or corticosteroids alone.¹¹ Another meta-analysis of four cohorts and seven clinical trials showed improvement in SNOT, as well as endoscopic and CT scores with macrolide therapy alone, compared to controls at eight weeks.¹⁹ In contrast with our findings, Videler and colleagues reported no significant difference between azithromycin and placebo for the treatment of CRS.¹³ This discrepancy can be explained by the difference in azithromycin dosages, treatment duration, study design, assessment method, and baseline severity of CRS. Furthermore, some patients in their study had asthma, and more than half had undergone revision sinus surgery.

The two classes of antibiotics that have been investigated for the treatment of CRS are macrolides (mainly azithromycin and clarithromycin) and tetracyclines (mainly doxycycline).⁵ The role of macrolides in the management of CRS has been attributed to their immunomodulatory properties (e.g., reduction of proinflammatory cytokines, oxidative damage, and neutrophil infiltration) rather than their antibacterial properties. Moreover, due to the ability of doxycycline to inhibit matrix metalloproteinase activity, it has been effective in CRS with nasal polyposis.⁵ *Staphylococcus aureus* and anaerobic organisms (*Prevotella* and *Porphyromonas*, *Peptostreptococcus* spp., and *Fusobacterium*) are the most common isolates in CRS.²⁰ Macrolides provide good coverage of Gram-positive cocci, as well as intracellular and atypical pathogens, but less effective against

Gram-negative bacteria, while doxycycline broadly covers both Gram-positive and some Gram-negative species.⁵

Mucociliary clearance is a critical component in the treatment of CRS. The role of macrolides in the production and clearance of mucus were indicated in previous studies on lower respiratory tract diseases such as bronchiectasis and chronic bronchitis.²¹⁻²³ In fact, sputum production was found to be reduced by half with clarithromycin. Reduction in viscosity and quantity as well as improved clearance of nasal secretions have also been shown in previous studies. Some studies demonstrated that mucociliary clearance improves with macrolides when objectively measured using the saccharin transit time (STT) test.²⁴⁻²⁶ However, the effectiveness of macrolides, especially azithromycin, in our study was due to their use in combination with conventional therapies. We found that conventional therapies significantly contributed to sinus drainage. We first used normal saline to irrigate sinonasal cavities followed by the administration of oxymetazoline spray, a sympathomimetic agent used as a decongestant²⁷ that aids the patency of the cavity. In addition, we used fluticasone spray as a topical steroid which is proven to improve symptoms and disease control in CRS. The spray acts as a safe anti-inflammatory agent with high clinical efficacy and few systemic effects and is easy to use.²⁸ Steam inhalation was the next step in alleviating obstruction,²⁹ aiding sinus drainage. Finally, we used guaifenesin syrup which is believed to have multiple mucolytic effects including an increase in secretion volume, reduction in mucus consistency and viscosity, and improved mucociliary clearance.³⁰ Another important component of the conventional therapies used in the current study was the use of long-acting betamethasone injections. The use of systemic corticosteroids can be effective in reducing the inflammatory response in CRS through different mechanisms. It can reduce the normal levels of circulating inflammatory cells by 20%. Histopathological examinations showed the abundance of eosinophils, a type of inflammatory cells, in the mucosa of patients with CRS. Anti-inflammatory effects of systemic corticosteroids mainly target eosinophils, namely through shortening eosinophil half-life, inhibition of eosinophil-specific cytokines, decreasing the number of circulating eosinophils, and inhibition of eosinophil migration to the sites of inflammation.³¹ Moreover, steroids can reduce cell proliferation, mucus secretion, vascular permeability, and chemotaxis, as they interfere with the enzymatic activity of phospholipase

A₂ leading to the inhibition of arachidonic acid production.³²

Cytochrome p450 pathways, specifically the enzyme CYP3A4, are responsible for the metabolism of most macrolides as well as interaction with other drugs that use the same pathway. Since azithromycin is not metabolized via this pathway, it has fewer drug interactions than other macrolides such as clarithromycin. Another advantage of azithromycin over clarithromycin is that the dosing of clarithromycin has to be adjusted in patients with low creatinine clearance, whereas no adjustments are required for azithromycin.⁵ However, an increased risk of hearing loss is associated with azithromycin in comparison with clarithromycin.³³

The anti-inflammatory properties of macrolides are largely due to their role in reducing pro-inflammatory cytokines, such as IL-8, which is a neutrophil chemoattractant.³⁴ This bears significance, because the same neutrophil inhibitory property is not seen with immunosuppressants such as corticosteroids frequently used as anti-inflammatory agents in CRS.³⁵

A previous study reported that the response to macrolide therapy for CRS becomes evident after a trial of at least 12 consecutive weeks.³⁶ Other studies have suggested that the clinical benefit of macrolide therapy may not be apparent until four to eight weeks of treatment.^{36, 37} However, as a strength of the current study, we showed that a four-week course of treatment with either of the macrolides was effective in the resolution of CRS symptoms. Prolonged QT interval leading to torsades de pointes was an important side effect of macrolides.³⁸ However, these fatal cardiac side effects seemingly did not extend beyond the period of administration.^{39, 40} A shorter treatment period with macrolides, as in our study, may help towards reducing their incidence.

The main strength of the current study is the comparison of two macrolides (azithromycin and clarithromycin) for the treatment of CRS. Moreover, combining the macrolides with conventional therapies appears to have increased the efficacy of the antibiotics. As a limitation, we could not assess the recurrence of CRS, since there was no long-term follow-up of the patients.

Conclusion

In combination with conventional therapies for CRS in adults, a four-week course of treatment with azithromycin is more effective than with clarithromycin. Conventional therapies played an important role in sinus drainage. Further

studies with larger sample sizes are required to confirm the advantages of azithromycin over clarithromycin.

Acknowledgment

We would like to thank all those involved in this research project, especially the patients, and the staff of the Otorhinolaryngology Clinic of Shahid Mohammadi Hospital for their contribution.

Author's Contribution

M.A: Designed the study and wrote the manuscript; M.K: Reviewed the CT scans and critically revised the final draft; G.Z: Analyzed and interpreted the data and contributed in writing the manuscript. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work and ensured that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Conflict of Interest: None declared.

References

- 1 Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg.* 2003;129:S1-32. doi: 10.1016/s0194-5998(03)01397-4. PubMed PMID: 12958561.
- 2 Sedaghat AR. Chronic rhinosinusitis. *Infections of the ears, nose, throat, and sinuses.* 2018:155-68. doi: https://doi.org/10.1007/978-3-319-74835-1_13.
- 3 Siu J, Klingler L, Wang Y, Hung CT, Jeong SH, Smith S, et al. Oral antibiotics used in the treatment of chronic rhinosinusitis have limited penetration into the sinonasal mucosa: a randomized trial. *Xenobiotica.* 2020;50:1443-50. doi: 10.1080/00498254.2020.1814973. PubMed PMID: 32840412.
- 4 Barshak MB, Durand ML. The role of infection and antibiotics in chronic rhinosinusitis. *Laryngoscope Investig Otolaryngol.* 2017;2:36-42. doi: 10.1002/lio2.61. PubMed PMID: 28894821; PubMed Central PMCID: PMC5510277.
- 5 Lees KA, Orlandi RR, Oakley G, Alt JA. The Role of Macrolides and Doxycycline in Chronic Rhinosinusitis. *Immunol Allergy Clin North Am.* 2020;40:303-15. doi: 10.1016/j.ia.2019.12.005. PubMed PMID: 32278453.
- 6 Aminov R. History of antimicrobial drug

- discovery: Major classes and health impact. *Biochem Pharmacol.* 2017;133:4-19. doi: 10.1016/j.bcp.2016.10.001. PubMed PMID: 27720719.
- 7 Shimizu T, Suzaki H. Past, present and future of macrolide therapy for chronic rhinosinusitis in Japan. *Auris Nasus Larynx.* 2016;43:131-6. doi: 10.1016/j.anl.2015.08.014. PubMed PMID: 26441370.
 - 8 Cervin A, Wallwork B. Macrolide therapy of chronic rhinosinusitis. *Rhinology.* 2007;45:259-67. PubMed PMID: 18085018.
 - 9 Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther.* 2014;143:225-45. doi: 10.1016/j.pharmthera.2014.03.003. PubMed PMID: 24631273.
 - 10 Margaritis VK, Ismailos GS, Naxakis SS, Mastronikolis NS, Goumas PD. Sinus fluid penetration of oral clarithromycin and azithromycin in patients with acute rhinosinusitis. *Am J Rhinol.* 2007;21:574-8. doi: 10.2500/ajr.2007.21.3071. PubMed PMID: 17999793.
 - 11 Huang Z, Zhou B. Clarithromycin for the treatment of adult chronic rhinosinusitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol.* 2019;9:545-55. doi: 10.1002/alr.22281. PubMed PMID: 30629811.
 - 12 Varvyanskaya A, Lopatin A. Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. *Int Forum Allergy Rhinol.* 2014;4:533-41. doi: 10.1002/alr.21318. PubMed PMID: 24659566.
 - 13 Videler WJ, Badia L, Harvey RJ, Gane S, Georgalas C, van der Meulen FW, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. *Allergy.* 2011;66:1457-68. doi: 10.1111/j.1398-9995.2011.02693.x. PubMed PMID: 21884529.
 - 14 Amali A, Saedi B, Rahavi-Ezabadi S, Ghazavi H, Hassanpoor N. Long-term postoperative azithromycin in patients with chronic rhinosinusitis: A randomized clinical trial. *Am J Rhinol Allergy.* 2015;29:421-4. doi: 10.2500/ajra.2015.29.4244. PubMed PMID: 26637580.
 - 15 Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc.* 2011;86:427-43. doi: 10.4065/mcp.2010.0392. PubMed PMID: 21490181; PubMed Central PMCID: PMC3084646.
 - 16 Hedeker D, Gibbons RD, Waternaux C. Sample size estimation for longitudinal designs with attrition: comparing time-related contrasts between two groups. *Journal of Educational and Behavioral Statistics.* 1999;24:70-93. doi: 10.3102/10769986024001070.
 - 17 Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? *Otolaryngol Head Neck Surg.* 2007;137:555-61. doi: 10.1016/j.otohns.2007.02.004. PubMed PMID: 17903570.
 - 18 Seresirikachorn K, Suwanparin N, Srisunthornphanich C, Chitsuthipakorn W, Kanjanawasee D, Snidvongs K. Factors of success of low-dose macrolides in chronic sinusitis: Systematic review and meta-analysis. *Laryngoscope.* 2019;129:1510-9. doi: 10.1002/lary.27865. PubMed PMID: 30746710.
 - 19 Shen S, Lou H, Wang C, Zhang L. Macrolide antibiotics in the treatment of chronic rhinosinusitis: evidence from a meta-analysis. *J Thorac Dis.* 2018;10:5913-23. doi: 10.21037/jtd.2018.10.41. PubMed PMID: 30505500; PubMed Central PMCID: PMC6236167.
 - 20 Brook I. Microbiology of chronic rhinosinusitis. *Eur J Clin Microbiol Infect Dis.* 2016;35:1059-68. doi: 10.1007/s10096-016-2640-x. PubMed PMID: 27086363.
 - 21 Hashiba M, Baba S. Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. *Acta Otolaryngol Suppl.* 1996;525:73-8. PubMed PMID: 8908275.
 - 22 Nishi K, Mizuguchi M, Tachibana H, Ooka T, Amemiya T, Myou S, et al. [Effect of clarithromycin on symptoms and mucociliary transport in patients with sino-bronchial syndrome]. *Nihon Kyobu Shikkan Gakkai Zasshi.* 1995;33:1392-400. PubMed PMID: 8821993.
 - 23 Tamaoki J, Takeyama K, Tagaya E, Konno K. Effect of clarithromycin on sputum production and its rheological properties in chronic respiratory tract infections. *Antimicrob Agents Chemother.* 1995;39:1688-90. doi: 10.1128/AAC.39.8.1688. PubMed PMID: 7486901; PubMed Central PMCID: PMC162808.
 - 24 Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope.* 2006;116:189-93. doi: 10.1097/01.mlg.0000191560.53555.08. PubMed PMID: 16467702.
 - 25 Cervin A, Kalm O, Sandkull P, Lindberg S. One-year low-dose erythromycin treatment

- of persistent chronic sinusitis after sinus surgery: clinical outcome and effects on mucociliary parameters and nasal nitric oxide. *Otolaryngol Head Neck Surg.* 2002;126:481-9. doi: 10.1067/mhn.2002.124849. PubMed PMID: 12075221.
- 26 Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope.* 2004;114:923-30. doi: 10.1097/00005537-200405000-00027. PubMed PMID: 15126758.
 - 27 Matreja P, Gupta V, Kaur J, Singh S. Efficacy of fluticasone and oxymetazoline as the treatment for allergic rhinitis. *J Clin Diagn Res.* 2012;6:85-8.
 - 28 Rudmik L, Hoy M, Schlosser RJ, Harvey RJ, Welch KC, Lund V, et al. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. *Int Forum Allergy Rhinol.* 2013;3:281-98. doi: 10.1002/alr.21096. PubMed PMID: 23044832.
 - 29 Vathanophas V, Pattamakajonpong P, Assanasen P, Suwanwech T. The effect of steam inhalation on nasal obstruction in patients with allergic rhinitis. *Asian Pac J Allergy Immunol.* 2021;39:304-8. doi: 10.12932/AP-090818-0393. PubMed PMID: 31175716.
 - 30 Seagrave J, Albrecht H, Park YS, Rubin B, Solomon G, Kim KC. Effect of guaifenesin on mucin production, rheology, and mucociliary transport in differentiated human airway epithelial cells. *Exp Lung Res.* 2011;37:606-14. doi: 10.3109/01902148.2011.623116. PubMed PMID: 22044398.
 - 31 Schleimer RP, Bochner BS. The effects of glucocorticoids on human eosinophils. *J Allergy Clin Immunol.* 1994;94:1202-13. doi: 10.1016/0091-6749(94)90333-6. PubMed PMID: 7798561.
 - 32 Burks AW, Holgate ST, O'Hehir RE, Bacharier LB, Broide DH, Hershey GKK, et al. *Middleton's allergy E-Book: principles and practice.* Amsterdam: Elsevier Health Sciences; 2019.
 - 33 Ikeda AK, Prince AA, Chen JX, Lieu JEC, Shin JJ. Macrolide-associated sensorineural hearing loss: A systematic review. *Laryngoscope.* 2018;128:228-36. doi: 10.1002/lary.26799. PubMed PMID: 28771738.
 - 34 Bachert C, Wagenmann M, Rudack C, Hopken K, Hillebrandt M, Wang D, et al. The role of cytokines in infectious sinusitis and nasal polyposis. *Allergy.* 1998;53:2-13. doi: 10.1111/j.1398-9995.1998.tb03767.x. PubMed PMID: 9491223; PubMed Central PMCID: PMCPMC7159491.
 - 35 Vanaudenaerde BM, Wuyts WA, Geudens N, Dupont LJ, Schoofs K, Smeets S, et al. Macrolides inhibit IL17-induced IL8 and 8-iso-prostane release from human airway smooth muscle cells. *Am J Transplant.* 2007;7:76-82. doi: 10.1111/j.1600-6143.2006.01586.x. PubMed PMID: 17061983.
 - 36 Nakamura Y, Suzuki M, Yokota M, Ozaki S, Ohno N, Hamajima Y, et al. Optimal duration of macrolide treatment for chronic sinusitis after endoscopic sinus surgery. *Auris Nasus Larynx.* 2013;40:366-72. doi: 10.1016/j.anl.2012.09.009. PubMed PMID: 23107100.
 - 37 Majima Y, Kurono Y, Hirakawa K, Ichimura K, Haruna S, Suzaki H, et al. Efficacy of combined treatment with S-carboxymethylcysteine (carbocysteine) and clarithromycin in chronic rhinosinusitis patients without nasal polyp or with small nasal polyp. *Auris Nasus Larynx.* 2012;39:38-47. doi: 10.1016/j.anl.2011.04.015. PubMed PMID: 21636230.
 - 38 Svanstrom H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study. *BMJ.* 2014;349:g4930. doi: 10.1136/bmj.g4930. PubMed PMID: 25139799; PubMed Central PMCID: PMCPMC4138354.
 - 39 Schembri S, Williamson PA, Short PM, Singanayagam A, Akram A, Taylor J, et al. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ.* 2013;346:f1235. doi: 10.1136/bmj.f1235. PubMed PMID: 23525864.
 - 40 Inghammar M, Nibell O, Pasternak B, Melbye M, Svanstrom H, Hviid A. Long-Term Risk of Cardiovascular Death With Use of Clarithromycin and Roxithromycin: A Nationwide Cohort Study. *Am J Epidemiol.* 2018;187:777-85. doi: 10.1093/aje/kwx359. PubMed PMID: 29155931.