Clarithromycin in the Management of Chronic Rhinosinusitis: Preliminary Results of a Possible Its New Use

F. Sireci¹ · R. Speciale¹ · S. Gallina¹ · R. Sorrentino² · F. R. Canevari²

Received: 1 November 2016 / Accepted: 17 July 2017 / Published online: 20 July 2017
© Association of Otolaryngologists of India 2017

Abstract The aim of this study is to evaluate the efficacy and safety of prolonged therapy with low-dose clarithromycin in patients with chronic rhinosinusitis with polyps (CRSwP) after endoscopic sinus surgery (ESS). A total of 10 patients with CRSwP were identified and subjected to bilateral ESS. In post-operative patients they were treated with nasal wash with saline solution and steroid sprays (beclomethasone). During follow-up, after 30–40 days after the operation ($M = 35.4$ $SD = +4.33$), patients reported a worsening of symptoms with onset of nasal obstruction; reduction/loss of smell; headache; onset of viscous secretions and therefore all patients continued therapy with saline nasal irrigation, topical steroid therapy and started macrolide (clarithromycin 500 mg/pill: 1 pill/day for 3 days a week for 1 month). 22-item SinoNasal Outcome Test (SNOT-22) and a score to the endoscopic evaluation (endoscopic appearance score, EAS) before and after treatment were performed to evaluate efficacy of treatment. The results of the SNOT-22 and EAS showed statistically significant improvements ($p < 0.05$) for some parameters such as: the need to blow nose, sneezing, hyposmia, viscous mucous secretions about the SNOT-22 and reduction of secretions and edema of the nasal mucosa about the EAS. The preliminary results of our study show that the low-dose clarithromycin for a period of 1 month

can improve patient complaints with CRSwP not only through the antibacterial properties but also for the immunomodulatory characteristics.

Keywords Chronic rhinosinusitis with polyps · Clarithromycin · Eosinophil

Introduction

Chronic rhinosinusitis (CRS) often occurs in association with nasal polyps (NP) in 4% of an entire population [1] and is associated with bronchial asthma (BA) in 7–13% of cases [2] and aspirin-exacerbated respiratory disease (AERD) and NP are present in 36–96% of patients [3]. In CRSwNP the predominate inflammatory cell is the eosinophil, which is found in both the tissue and in the airway mucus. The role of neutrophilic inflammation has been investigated but it does not seem to be a primary factor in the development of CRSwNP although the correlation with BA. Allergy seems to be a comorbid condition and not a primary factor in the development of CRSwNP [4–6]. At present, neither medical nor surgical treatment can ensure permanent control or enduring cure. Currently the only proven treatment for effective control of CRSwNP is topical nasal steroid sprays with or without systemic glucocorticosteroids (GCS). Recurrent CRSwNP is not always prevented even with systemic GCS and the side effects can be serious [7]. Because disease control can be difficult even with systemic GCS we decided to study treatment with “long-term” therapy using low dose macrolide antibiotics. The rational use of this drug does not reside in its antimicrobial properties as much as in its anti-inflammatory effects by inhibition of neutrophils and eosinophils. The macrolides are capable of modulating the immune

✉ F. Sireci
federicosireci@hotmail.it

¹ Otorhinolaryngology Section, Department of Experimental Biomedicine and Clinical Neurosciences, (BioNeC), University of Palermo, via del Vespro 129, 90127 Palermo, Italy

² Otorhinolaryngology Section, SS Antonio Biagio e Cesare Arrigo Hospital, Alessandria, Italy

response, inhibiting polyp growth, destroying biofilms, and enhancing the protective properties of the respiratory tract mucosa [8–11]. Macrolide effectiveness in patients with CRS without NP has been confirmed; however, their efficacy in CRSwNP patients has not been thoroughly investigated [4]. Therefore, our study was designed to evaluate the efficacy and safety of a long-term course of low-dose clarithromycin therapy in patients with CRSwNP after endoscopic sinus surgery (ESS) [12, 13].

Materials and Methods

A total of 10 patients affected by CRSwNP were identified at the Section of Otolaryngology of SS Antonio Biagio e Cesare Arrigo Hospital, Alessandria between October 2015 and May 2016. The inclusion criteria were: nasal obstruction; reduction/loss of smell; headache; bilateral nasal polyps; viscous nasal secretions; peripheral blood eosinophilia; presence of asthma and/or intolerance to aspirin and/or atopy; eosinophilia in nasal polyps highlighted by 'histological examination. Exclusion criteria included the following: unilateral CRSwNP, macrolide intolerance, use of systemic steroids, pregnancy, lactation, and severe somatic diseases. Selected patients had an age between 24 and 69 years ($M = 40$; $SD = \pm 16.06$). Informed consent was obtained from each patient. Four patients were male and twelve female. All patients were examined with a fiberoptic and cranio-facial CT computerised tomography (CT). All 10 patients underwent bilateral ESS performed by the same surgeon.

The nasal pack was removed the day after and the patient discharged. Seven days of antibiotics therapy amoxicillin/clavulanate combination, saline nasal irrigation and application of gomenolato oil spray was recommended. Patients were carefully followed and seen at 1 week intervals after ESS for medication. At 4–21 days after surgery ($M = 18.1$; $SD = + 3.06$), patients showed resolution of scabs and scars, and therefore they were started on topical steroid (beclomethasone) and continued saline nasal irrigation. At 30–40 days after surgery ($M = 35.04$ $SD = \pm 4.33$), patients reported a worsening of symptoms with onset of nasal obstruction; reductions/loss of smell; headache; high viscous secretions and therefore all patients continued therapy with saline nasal irrigation, topic steroid and started clarithromycin 500 mg/die for 3 days at week for 1 month.

Results of treatment were based on evaluation of 22-item SinoNasal Outcome Test (SNOT-22) and a score to the nasal endoscopy (endoscopic appearance score, EAS) recorded before and after therapy with clarithromycin.

The 20-item SinoNasal Outcome Test (SNOT-20) is a questionnaire for evaluating the quality of life (QoL) in rhinosinusitis patients [14].

Endoscopy was performed with rigid fiberoptic endoscope 4 mm (Karl Storz, Tuttlingen, Germany) after decongestion of the nasal nostrils with cotton soaked in adrenaline and mepivacaine. EAS was given to the following endoscopic findings evaluated for both nasal cavities [15]: (1) the polyps were graded by size from 0 to 3 (0 = no polyps; 1 = polyps that appear only in the meatus medium; 2 = polyps extending beyond the middle meatus but not obstructing the nose; 3 = polyps completely obstructing the nose); (2) Discharge was scored as follows: 0 = no discharge; 1 = poor and clear discharge; 2 = dense and mucosal secretion; (3) the mucosal edema was assessed as follows: 0 = absent; 1 = mild; 2 = severe; (4) Postoperative Crusts and scars have received the following score: 0 = absent; 1 = mild; and 2 = severe.

Statistical Analysis

The results obtained were entered into a computerized database and processed using the statistical software package SPSS version 17.0 for Windows. T student signed rank tests were performed to evaluate significant difference before and after use of clarithromycin. Values were presented as means $\pm$ standard deviations. Results were considered statistically significant when p values were <0.05 .

Results

90% (9/10) patients had BA, and 40% (4/10) presented with AERD. Atopy was confirmed by skin prick tests in 70% (7/10). Side effects related to clarithromycin were not evidenced. The results of the SNOT-22 and EAS evaluated before and after treatment with clarithromycin showed statistically significant improvements ($p < 0.05$) for some parameters.

In particular, SNOT-22 showed an improvement about: blowing the nose (2.52 ± 0.87 vs. 1.3 ± 0.67), sneezing (2.1 ± 0.99 vs. 0.7 ± 0.94), hyposmia (3.1 ± 1.4 vs. 1.7 ± 1.49), dense mucous discharge (3.5 ± 1.17 vs. 1.5 ± 0.97) (Table 1). EAS evaluated before and after treatment with clarithromycin showed improvements in particular for two parameters: secretions (1.6 ± 0.69 vs. 0.3 ± 0.48) and edema (1.3 ± 0.48 vs. 0.2 ± 0.42) (Table 2).

6 months after treatment with clarithromycin, no patients reported a worsening of symptoms and the SNOT-22 and EAS showed no significant changes compared to those performed at the end of therapy with clarithromycin.

Table 1 20-item SinoNasal Outcome Test (SNOT-20) evaluation pre and post therapy with clarithromycin

SNOT 22	Pre (M ± SD)	Post (M ± SD)	T-student	p value
Need to blow your nose	2.5 (±0.8)	1.3 (±0.6)	3.5	0.002*
Sneezing	2.1 (±0.9)	0.7 (±0.9)	3.2	0.004*
Runny nose	1.3 (±1.5)	0.6 (±0.7)	0.93	0.35
Blockage/congestion of nose	2.2 (±1.9)	1 (±1)	1.68	1.10
Sense of smell	3.1 (±1.4)	1.7 (±1.5)	2.12	0.04*
Cough	1.2 (±1.5)	0.7 (±0.9)	0.90	0.37
Post nasal discharge	1.7 (±2)	0.9 (±1.2)	1.08	0.29
Thick nasal discharge	3.5 (±1.2)	1.5 (±0.9)	4.14	0.0006*
Ear fullness	1 (±1.4)	0.4 (±0.7)	1.20	0.24
Dizziness	0.3 (±0.6)	0.2 (±0.6)	0.34	0.73
Ear pain	0.4 (±0.5)	0.4 (±0.5)	0	1
Headache	0.7 (±1.5)	0.5 (±0.9)	0.34	0.73
Difficult falling asleep	0.3 (±0.7)	0.2 (±0.4)	0.39	0.69
Waking up at night	1.3 (±1.4)	0.7 (±0.8)	1.15	0.26
Lack of a good night's sleep	1 (±1.3)	0.6 (±0.8)	0.80	0.43
Waking up tired	1.4 (±1.4)	0.7 (±0.8)	1.34	0.19
Fatigue during the day	1.7 (±1.6)	0.7 (±0.5)	2.02	0.057
Reduced productivity	1.3 (±1.2)	0.5 (±0.7)	1.75	0.09
Reduced concentration	1.7 (±1.2)	0.9 (±0.9)	1.58	0.13
Irritable	3.09 (±1.4)	1 (±1)	0.53	0.59
Sad	1 (±0.9)	0.6 (±0.7)	1.07	0.29
Embarrassed	0.5 (±0.9)	0.3 (±0.7)	0.53	0.59

M media, SD standard deviation

* Significant differences between study and control groups ($p < 0.05$)

Table 2 Endoscopic Appearance Score Evaluation (EAS) pre and post therapy with clarithromycin

EAS	Pre (M ± SD)	Post (M ± SD)	T-student	p value
Polyps (0–3)	1 (±0.5)	1.3 (±0.6)	0.55	0.58
Secretions (0–2)	1.6 (±0.7)	0.7 (±0.9)	4.8	0.00001*
Edema (0–2)	1.3 (±0.5)	0.6 (±0.7)	5.4	0.00001*
Scabs and scars (0–2)	0	0	–	–

M media, SD standard deviation

* Significant differences between study and control groups ($p < 0.05$)

Discussion

Our results suggest that a prolonged treatment with low-dose clarithromycin is effective when reserved for patients with recalcitrant CRS linked with BA and/or AERD and/or atopy in whom ESS associated with topical steroid therapy and nasal irrigation is not sufficient.

Although the mechanisms of CRSwP are not completely understood, the dysfunction of the mucosa of the paranasal sinuses seems to have a central role. The histopathological features of CRSwP are an increase of submucosal glands, a

ciliated epithelium transformation in squamous epithelium and an infiltration of inflammatory cells such as neutrophils and eosinophils [16]. Fujita et al. [17] reported increased nasal concentration of IL-8 in cases with CRSwP compared to healthy subjects. In chronic rhinosinusitis, pus and viscous mucus in the sinuses together with bacteria act mucosal epithelium to produce pro-inflammatory cytokines such as IL-8. These cytokines induce a neutrophilic and eosinophilic infiltration, damage the ciliated epithelium and increasing the number of submucosal glands. This creates a vicious circle with chronic inflammation. Fujita

Table 3 Protocol therapy of clarithromycin present in literature

References	Drug	Dose/duration	No. patients	Started	Evaluated parameters
Peric et al. [25]	Clarithromycin	500 mg/day for 2 months	40	First postoperative day	Cytokines
Nakamura et al. [26]	Clarithromycin	200 mg/day for 6 months	66	1 week after surgery	VAS
Varvyanskaya and Lopatin [20]	Clarithromycin	200 mg/day for 6 months	66	First postoperative day	VAS ECP
Sireci et al. (Present article)	Clarithromycin	500 gm/die for 3 days at week for 1 month	10	35.04 days after surgery	SNOT-20 EAS

VAS Visual Analogue Scale, ECP eosinophil cation protein, SNOT-20 = 20-item SinoNasal Outcome Test, EAS Endoscopic Appearance Score Evaluation

et al. [17] has shown that the macrolide administered for 3 months significantly reduces the concentration of neutrophils, eosinophils and IL-8 in the nasal secretion. Wallwork et al. [18], using roxithromycin 150 mg in patients with CRSwP, reported in the saccharine test a significant reduction from 11.5 to 8.2 min before and after treatment, demonstrating the recovery of mucociliary clearance. In spite of good results of macrolides therapy, literature is uniformly agreed to combine medical therapy with endoscopic sinus surgery normalizing pathological mucosa and removing the viscous mucus that contains bacteria and pro-inflammatory molecules. Inanli et al. [16] has conducted the test with saccharin, before and after surgery and showed that the mucociliary function significantly improved after surgery (respectively 12:15 min and 9:08 min before and after surgery). However, the ciliated epithelium was only partially restored, and the pathological mucosa was still present 3 months after surgery.

Fang [19] did endoscopic examination of the epithelium of maxillary sinus in 121 patients and evaluated that the time necessary for its normalization was between 9 and 12 weeks, however, in 32 patients it took more than 12 weeks and in 16 it had not reached normalization with persistence of polyps and edema even after 16 weeks. It can be deduced that the regeneration of epithelium is still ongoing to 3–6 months after surgery. The reason for this slow recovery is the fact that the surgery itself causes a eosinophilic inflammation that often can not be adequately controlled with topical nasal steroids. In fact, Varvyanskaya and Lopatin studied the change of the levels of ECP (eosinophil cationic protein) in nasal secretions after FESS and after macrolide therapy. In the control group (not treated with macrolide) an increase of 3 times the average level ECP to 6 weeks after surgery while in the group treated with macrolide there was a gradual decrease in the levels of ECP [20].

Therefore macrolide may reduce postoperative inflammation caused by the surgery, promote earliest possible

normalization of pathological mucosa and improvement in symptoms.

Problem discussed in the literature is the correct duration of treatment with the macrolide (Table 3). Kikuchi et al. [21] has shown that the long-term low-dose treatment with erythromycin 400–600 mg was effective in patients with symptomatic chronic sinusitis. In their study, the runny nose was reduced in 60% of cases, postnasal drip in 50%, nasal obstruction in 60% and headache in 100%. However, the duration of treatment has not been established (3–19 months), and the average duration was 7.9 months. Subsequently, Hashiba and Baba [22] administered macrolide 400 mg for more than 12 weeks and showed an improvement in 70.6% of patients at 12 weeks but concluded that still remained uncertainty about the safety of the drug with a prolonged administration and that treatment should not be extended when the symptoms are relieved. The duration of treatment in the majority of subsequent studies was 3 months with results comparable to our protocol of 1 month of treatment even though the our short follow-up (6 months) not allow to establish how long the beneficial effects of macrolide are maintained. Nevertheless our clarithromycin protocol can be more manageable and can be used again whenever there is recurrence of symptoms. A prolonged treatment with the macrolide not only improves significantly symptoms such as nasal respiratory obstruction and headache and, therefore, a month of therapy is sufficient avoiding systemic corticosteroids (GS) that lead to different side effects.

The macrolide antibiotics are also excellent and have an important role not only in the treatment of Mycoplasma and Chlamydia but also in the eradication of Helicobacter pylori which has been reported as a cause of chronic gastritis. Furthermore a prolonged treatment with antibiotic can lead to antimicrobial resistance although currently in the literature was shown that there is not an increase of bacteria resistant to macrolides in cultures of samples taken from the middle meatus [23, 24].

Conclusion

The preliminary results of our study show that the low-dose clarithromycin for a period of 1 month can improve patients with eosinophilic chronic rhinosinusitis disorders not only through the antibacterial properties but also for the immunomodulatory characteristics.

Using case–control double-blind study and a large size of cases, the efficacy of long term macrolide use in prevention of nasal polyposis recurrence after ESS needs to be determined and a treatment protocol has to be validated internationally for wider usage.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest in the preparation of this article.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

References

- Hedman J, Kaprio J, Poussa T, Nieminen MM (1999) Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 28:717–722
- Settipane G (1997) Epidemiology of nasal polyps. In: Settipane G, Lund VJ, Bernstein JM, Tos M (eds) *Nasal polyps: epidemiology, pathogenesis and treatment*. Oceanside Publications, Providence, pp 17–24
- Ogino S, Harada T, Okawachi I, Irifune M, Matsunaga T, Nagano T (1986) Aspirin-induced asthma and nasal polyps. *Acta Otolaryngol Suppl* 430:21–27
- Fokkens W, Lund V, Mullol J (2007) European position paper on rhinosinusitis and nasal polyps group. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 20:1–136
- Martines F, Salvago P, Ferrara S, Messina G, Mucia M, Plescia F et al (2016) Factors influencing the development of otitis media among Sicilian children affected by upper respiratory tract infections. *Braz J Otorhinolaryngol* 82(2):215–222
- Martines F, Salvago P, Ferrara S, Mucia M, Gambino A, Sireci F (2014) Parietal subdural empyema as complication of acute odontogenic sinusitis: a case report. *J Med Case Rep* 21(8):282
- Desrosiers MY, Kilty SJ (2008) Treatment alternatives for chronic rhinosinusitis persisting after ESS: what to do when antibiotics, steroids and surgery fail. *Rhinology* 46:3–14
- Kudoh S, Uetake T, Hagiwara K, Hirayama M, Hus LH, Kimura H et al (1984) Clinical effect of low-dose, long-term erythromycin chemotherapy on diffuse panbronchiolitis (English Abstract). *Jpn J Thorac Dis* 25:632–642
- Kudoh S, Asuma A, Yamamoto M, Izumi T, Ando M (1998) Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 157:1829–1832
- Cervin A, Wallwork B (2007) Macrolide therapy of chronic rhinosinusitis. *Rhinology* 45:259–267
- Cervin A, Wallwork B, Mackay-Sim A, Coman WB, Greiff L (2009) Effects of long-term clarithromycin treatment on lavage-fluid markers of inflammation in chronic rhinosinusitis. *Clin Physiol Funct Imaging* 29:136–142
- Canevari FR, Giourgos G, Pistochini A (2014) The endoscopic transnasal paraseptal approach to a sphenoid sinus osteoma: case report and literature review. *Ear Nose Throat J*. 2013 Dec; 92(12): E7–E10. Review. Erratum in: *Ear Nose Throat J* 93(4–5):148
- Vitali M, Canevari FR, Cattalani A, Grasso V, Somma T, Barbanera A (2016) Direct fascia lata reconstruction to reduce donor site morbidity in endoscopic endonasal extended surgery: a pilot study. *Clin Neurol Neurosurg* 144:59–63
- Piccirillo J, Merritt M, Richards M (2001) Psychometric and clinimetric validity of the 20-item Sino-Nasal Outcome Test (SNOT-20). *Otolaryngol Head Neck Surg* 126:41–47
- Lund VJ, Mackay IS (1993) Staging in rhinosinusitis. *Rhinology* 31:183–184
- Inanli S, Tutkun A, Batman C, Okar I, Uneri C, Sehitoglu MA (2000) The effect of endoscopic sinus surgery on mucociliary activity and healing of maxillary sinus mucosa. *Rhinology* 38:120–123
- Fujita K, Shimizu T, Majima Y, Sakakura Y (2000) Effects of macrolides on interleukin- 8 secretion from human nasal epithelial cells. *Eur Arch Otorhinolaryngol* 257:199–204
- Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A (2006) A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope* 116:189–193
- Fang SY (1994) Normalization of maxillary sinus mucosa after FESS. A prospective study of chronic sinusitis with nasal polyps. *Rhinology* 32:137–140
- Varvyanskaya A, Lopatin A (2014) Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. *Int Forum Allergy Rhinol* 4(7):533–541
- Kikuchi S, Susaki H, Aoki A, Ito O, Nomura Y (1991) Clinical effect of long-term lowdose erythromycin therapy for chronic sinusitis. *Pract Otol* 84:41–47
- Hashiba M, Baba S (1996) Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. *Acta Otolaryngol Suppl* 525:73–78
- Videler WJ, Badia L, Harvey RJ, Gane S, Georgalas C, van der Meulen FW et al (2011) Lack of efficacy of long term, low-dose azithromycin in chronic rhinosinusitis: randomized controlled trial. *Allergy* 66:1457–1468
- Cervin A, Kalm O, Sandkull P, Lindberg S (2002) 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* 126:481–489
- Peric A, Vojvodic D, Baletic N, Peric A, Miljanovic O (2010) Influence of allergy on the immunomodulatory and clinical effects of long-term low-dose macrolide treatment of nasal polyposis. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 154:327–333
- Nakamura Y, Suzuki M, Yokota M, Ozaki S, Ohno N, Hamajima Y et al (2013) Optimal duration of macrolide treatment for chronic sinusitis after endoscopic sinus surgery. *Auris Nasus Larynx* 40:366–372