Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

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ORIGINAL ARTICLE AIRWAY DISEASES

Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial

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To cite this article: Videler WJ, Badia L, Harvey RJ, Gane S, Georgalas C, van der Meulen FW, Menger DJ, Lehtonen MT, Toppila-Salmi SK, Vento SI, Hytönen M, Hellings PW, Kalogjera L, Lund VJ, Scadding G, Mullol J, Fokkens WJ. Lack of Efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. *Allergy* 2011; **66**: 1457–1468.

Keywords
antibiotic treatment; azithromycin; chronic rhinosinusitis; long-term low dose; nose diseases; nasal polyps; oral administration; paranasal sinus diseases; randomized controlled trial; sinusitis.

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Accepted for publication 26 July 2011

DOI:10.1111/j.1398-9995.2011.02693.x

Edited by: Anthony Frew

Abstract

Background: In persistent chronic rhinosinusitis (CRS), conventional treatment is often insufficient. Long-term, low-dose administration of macrolides has been suggested as a treatment option. The MACS (Macrolides in chronic rhinosinusitis) study is a randomized placebo-controlled trial evaluating the efficacy of azithromycin (AZM) in CRS.

Methods: We describe a group of patients with recalcitrant CRS with and without nasal polyps unresponsive to optimal medical and (in 92% also) surgical treatment. Patients were treated with AZM or placebo. AZM was given for 3 days at 500 mg during the first week, followed by 500 mg per week for the next 11 weeks. Patients were monitored until 3 months post-therapy. The assessments included Sino-Nasal Outcome Test-22 (SNOT-22), a Patient Response Rating Scale, Visual Analogue Scale (VAS), Short Form-36 (SF-36), rigid nasal endoscopy, peak nasal inspiratory flow (PNIF), Sniffin' Sticks smell tests and endoscopically guided middle meatus cultures.

Results: Sixty patients with a median age of 49 years were included. Fifty per cent had asthma and 58% had undergone revision sinus surgery. In the SNOT-22, Patient Response Rating Scale, VAS scores and SF-36, no significant difference between the AZM and the placebo groups was demonstrated. Nasal endoscopic findings, PNIF results, smell tests and microbiology showed no relevant significant differences between the groups either.

Conclusion: At the investigated dose of AZM over 3 months, no significant benefit was found over placebo. Possible reasons could be disease severity in the investigated group, under-dosage of AZM and under-powering of the study. Therefore, more research is urgently required.

Chronic rhinosinusitis (CRS) is defined in the European Position Paper on rhinosinusitis and nasal polyps (EP^{3}OS) as the presence of two or more symptoms of which one should be either nasal blockage/congestion or nasal discharge combined with facial pain/pressure and/or reduction/loss of smell for more than 12 weeks (1). This definition is completed with accompanying nasal endoscopic signs and/or corresponding mucosal changes on CT scan. In the last decades, the management of CRS has improved substantially. According to the EP^{3}OS-management-schemes, patients with CRS are primarily treated with nasal saline irrigation, intranasal corticosteroids and in more severe cases with antibiotics and/or systemic corticosteroids, especially when nasal polyps are prominent. In patients who do not optimally respond to this

strategy, endoscopic sinus surgery (ESS) is indicated. Primary ESS has success rates up to 75–98% (2–6).

Because CRS could be considered as a mucosal disease, with participation of the underlying bone in severe disease or occasionally after surgery, it is often necessary to continue medical treatment postoperatively. This may include long-term, low-dose antibiotics. In research, most attention, especially *in vitro*, has centred on the antibiotics of the macrolide family. Besides their antimicrobial effects, macrolides are thought to have anti-inflammatory or immunomodulatory capacities based on the blockage of the production of cytokines, such as interleukin-8 (IL-8) and tumour necrosis factor-α (TNF-α), combined with the effects on neutrophil migration and adhesion, and modulation of synthesis and secretion of mucus (7, 8). Few studies have examined the efficacy of long-term, low-dose antibiotics in CRS. The majority of the uncontrolled investigations have evaluated macrolides using varying outcome measures and have suggested clinical benefit. Improvement in symptoms and endoscopic findings (9), decrease in polyp size (10), improvement in radiological degree of mucosal changes in the sinuses on CT scan and reduction in neutrophils and IL-8 levels in nasal discharge (11) have been reported. Others have presented data on the improvement in saccharine transit time, nasal endoscopic examination and Visual Analogue Scale for congestion, runny nose, sticky secretion and headache (12). In a prospective, randomized controlled trial (RCT) comparing medical and surgical therapy for patients with CRS, prolonged treatment with antibiotics and ESS were equally effective up to 1 year (13). In the first-performed, double-blinded, randomized, placebo-controlled trial on the efficacy of 3 months of macrolide treatment in 64 patients with CRS, no significant differences were found. However, a significant benefit of macrolides over placebo was shown in a subpopulation of patients with low immunoglobulin E (IgE) level. In this subgroup, Sino-Nasal Outcome Test-20 (SNOT-20), nasal endoscopy, saccharine transit time and IL-8 levels in nasal lavage fluid improved in the antibiotic arm compared with placebo (14). In a recent RCT on the efficacy of methylprednisolone and a member of another antibiotic family (doxycycline) in 47 patients, a significant effect on nasal polyp size, nasal symptoms, and mucosal and systemic inflammation markers was demonstrated in both treatment arms (15).

In an attempt to further evaluate the use of macrolides in the treatment for CRS, especially in patients with recalcitrant disease, we designed the MACS trial (macrolides in chronic sinusitis). It is a prospective, double-blinded, randomized, placebo-controlled, international, multicentre trial on the efficacy of azithromycin (AZM) in patients with recalcitrant CRS. To date, this is only the second RCT on prolonged antibiotic treatment in patients with CRS.

Patients and methods

Patients

Patients between 18 and 70 years of age were enrolled in this study after signing the informed consent form. They all met the CRS criteria outlined in the EP^{3}OS definition for moderate-to-severe CRS. Their symptoms in combination with endoscopic signs and/or changes on CT scan completed the diagnosis of CRS. All patients had shown the absence of response to standard treatment regimes such as nasal saline irrigation combined with intranasal corticosteroids (>6 weeks) and short courses of antibiotics (<2 weeks), and most patients had already undergone ESS. Massive polyp (over grade 2) was an exclusion criterion. When performed, the last surgical procedure had to be more than 6 months prior to enrolment. A recent CT scan of the sinuses <6 months before the start had to show a minimum Lund–Mackay score of five on the worse side of the paranasal sinus system (16). CT scans were made for diagnostic purposes only.

Patients were encouraged to use saline irrigation for the nose twice daily. Intranasal or pulmonary steroids were allowed as long as the dosage was kept constant throughout study participation (a maximum of two times the regular dose was accepted). Important medication-linked exclusion criterion was the use of systemic antibiotics and/or systemic corticosteroids within 4 weeks before the start of the study. Patients with a known history of hypersensitivity to macrolides, or those using medication known to have had a reaction to members of the macrolide family, could not be enrolled in the study. Other inclusion and exclusion criteria are shown in Table 1.

Study design

This international study was designed as a double-blinded, randomized, placebo-controlled trial in six tertiary referral centres in Amsterdam, Helsinki, Leuven, London, Tampere and Zagreb. It was registered with the European Clinical Trials Database (EudraCT number 2005-001062-14). Full ethical approval was granted from all the local research and ethics committees of the participating centres. Patients were enrolled at the outpatient clinic by otorhinolaryngologists. The randomized, numbered study medication was kindly provided by the pharmaceutical company PLIVA (Zagreb, Croatia). Study medication was allocated per centre in two randomized blocks, containing six packs of treatments each. Qualified subjects were given study medication with consecutive numbering. Envelopes with corresponding numbering containing the content of each box were available in case of adverse events. To standardize data collection, all centres followed the MACS study protocol and archived the data in the MACS Clinical Record Form. Patients were treated with study medication for 3 months and were assessed after 6 and 12 weeks within this treatment period. Two weeks after the end of the treatment, the final visit was performed. A follow-up 3 months later was performed by telephone.

Study medication

Patients received the randomized trial medication containing either AZM or placebo. AZM is an azalide, a subclass of macrolide antibiotics. It acts by binding to the 50S ribosomal subunit of susceptible microorganisms and interfering with

Table 1 Inclusion and exclusion criteria of the MACS trial

Inclusion criteria	Exclusion criteria
Diagnosis of moderate/severe chronic rhinosinusitis (according to the EP^{3}OS definition)	Hypersensitivity to macrolides
Age ≥18 and ≤70 years	Systemic antibiotic or steroid treatment <1 month before, or during the study
Absence of response to standard treatment regimes like saline irrigation, intranasal corticosteroids (>6 weeks), short courses of antimicrobials (<2 weeks), or when performed endoscopic sinus surgery. After treatment, patients returned to the outpatient clinic with subjective complaints and objectified with signs at nasal endoscopy	Use of drugs suspected to interact with macrolide antibiotics
Subjects had to be >6 months after the last surgical procedure on the nose and sinuses, when performed	Administration of homeopathica to the nose
Sinus CT scan score ≥5 at the worst side (partial or total opacification) according to the Lund Mackay scoring system. CT scan had to be performed within 6 months before randomization. If subjects had undergone infundibulotomy and the infundibulum was open at the worst side, a score of ≥3 was required	Severe obstructive, bilateral nasal polyps under the middle turbinate
Willing to give informed consent and to adhere to visit schedules and medication restrictions	Subjects in whom the infection can be explained by cystic fibrosis or congenital mucociliary problems (e.g. primary ciliary dyskinesia)
Adequate contraceptive precautions in subjects with child-bearing potential	Known systemic vasculitis or granulomatous disease
	AIDS or known HIV positivity
	Severe septal deviation
	Craniofacial malformations
	Abnormalities requiring other modalities of therapy (obstructive nasal polyps, tumors and infection of dental origin)
	Impaired hepatic function or hepatic disease.
	Pregnancy or child-bearing potential not using adequate contraceptive precautions
	Subject not able to give informed consent (psychiatric/addictive disorder)
	Enrolment in other drug trials

microbial protein synthesis, besides the immunomodulatory capacities. Following oral administration, AZM achieves relatively low serum concentrations but shows rapid and extensive distribution into tissues, resulting in high tissue concentrations. AZM also has long terminal elimination half-life, and tissue concentrations are maintained well beyond the serum levels decline (17). Concentrations are even higher in infected tissue, because AZM is transported to the site of infection by phagocytic delivery (18–20). As tissue concentrations are maintained for 5–7 days after cessation, a once-daily dosing regimen of AZM should elevate concentrations in tissues persistently and should be sufficient in most infections (17, 20–23). In the MACS trial, AZM was given for 3 days at 500 mg during the first week, followed by 500 mg per week for the next 11 weeks. The placebo arm received the same amount of tablets, identical in appearance. The total period of treatment was 12 weeks. Hepatic function was monitored after 6 and 12 weeks during the use of the study medication. This treatment regime was completed with nasal saline irrigation twice daily.

Subjective measures

Subjective signs and symptoms of CRS, as well as quality of life, were evaluated at the assessment visits. The primary outcome measure was the SNOT-22. This is a rhinosinusitis evaluation instrument, in which patients answer 22 questions regarding their sinonasal symptoms (24, 25).

Several secondary outcome measures were assessed. A Patient Response Rating Scale was used to classify the subjective effect of the course [−2: desperately worse (deterioration of symptoms with significant impact on normal life); −1: worse (compared with the pretreatment situation); 0: no change; 1: improvement (although symptoms are present, they are scarcely troublesome); and 2: cured (virtually no symptoms present)].

The Visual Analogue Scale (VAS) grades symptoms on a 10-cm line. Zero (at the left end of the line) represents no complaints and 10 (at the right end) the worst possible symptoms. The following symptoms were assessed: headache, nasal obstruction, rhinorrhea, postnasal drip, feeling of

fullness, smell disturbance, facial pain, toothache, tears, coughing, nasal bleeding, crusts, general health, fatigue, nausea, vomiting and diarrhoea.

Short Form-36 (SF-36) is a widely used, reproducible and valid generic quality of life measure, which evaluates general health status by grouping 36 item responses into eight health domains as follows: physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH) (26–29).

Objective measures

The nasal cavity was evaluated by rigid nasal endoscopy. Scoring was carried out according to a template that graded mucosal colour (0, normal; 1, abnormal), mucosal swelling (0, no swelling; 1, mild swelling; 2, severe swelling), nasal secretions (0, normal; 1, abnormal) and polyps (0, absent; 1, mild; 2, severe). Postnasal drip (0, absent; 1, present) and crusts (0, absent; 1, mild; 2, severe) were also evaluated.

Peak nasal inspiratory flow (PNIF) was performed on every visit. The best of three inhalations was recorded (30).

Olfactory function was tested using the Sniffin' Sticks odour identification screening test (Burghardt, Wedel, Germany). In this test, 12 pens with different odours were presented and the subject has to choose the correct answer from a multiple-choice form. The maximum score was 12 (0–6 reflects anosmia, 7–10 hyposmia and 11–12 normosmia) (31).

Endoscopically guided middle meatus cultures were prepared at the start and after the treatment, to evaluate bacterial colonization. A pretreatment CT scan of the paranasal sinuses was taken and scored using the Lund–Mackay scoring system (16).

Statistical analysis

All data were entered into a computerized database, and analysis was conducted using statistical software package SPSS version 16.0 statistical software (Amsterdam, The Netherlands), after consulting a medical statistician. To analyse the primary outcome of SNOT-22, we performed an area under the curve (AUC) analysis with Mann–Whitney *U*-test. SNOT-22, Patient Response Rating scale and the VAS scores were analysed first by calculating delta scores (score on a time point minus the pretreatment baseline score). These delta scores were analysed using the Mann–Whitney *U*-test. The SF-36 questionnaire was analysed using mixed-model analysis. The nasal endoscopic findings were analysed using chi-square test for trend. Peak nasal inspiratory flow and smell test results were analysed using Mann–Whitney *U*-tests. Bacteriological data were evaluated using the chi-square test and McNemar tests.

Results

Patient characteristics

A total of 60 patients with CRS according to the EP^{3}OS definition were identified and included (see Fig. 1). All enrolled patients were unresponsive to conventional medical treatment

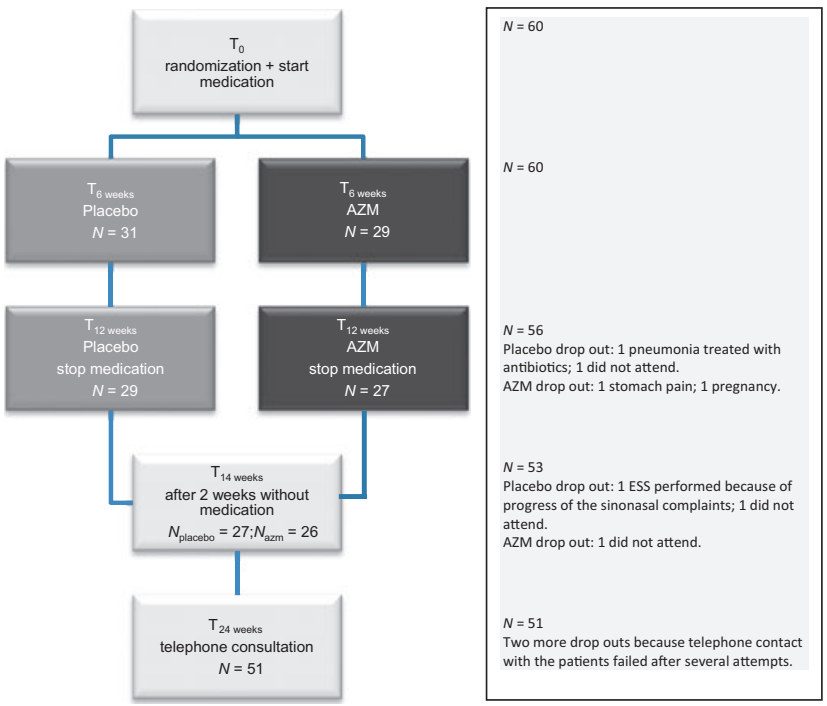

Figure 1 Patient flow chart of the MACS clinical trial.

Table 2 Patient characteristics

	Total	Azithromycin	Placebo
Number of patients	60 patients	29	31
Medium age	49 years (20–70 years)	49	49
Male:Female	30:30 patients	17:12	13:18
Caucasian: Asian	56:4 patients	26:3	30:1
Active smoker	5 patients (8%)	1	4
Alcohol	32 patients (53%)	15	17
Positive skin prick test	29 patients (48%)	14	15
Asthma	30 patients (50%)	15	15
Nasal polyps	31 patients (52%)	18	13
Intranasal steroids	42 patients (70%)	19	23
Inhaled steroids	28 patients (47%)	12	16
Revision surgery	35 patients (58%)	16	19
Mean number of endoscopic sinus surgery per patient	2.5	1.8	3.1
Lund–Mackay score	13.5 (maximum of 24)	14.5	13

and returned to the outpatient clinic with subjective sinonasal complaints, objectified with rigid nasal endoscopy. Fifty-five patients (92%) had undergone sinonasal surgery in the past in an attempt to relieve the CRS symptoms. These patients had undergone a mean number of 2.5 earlier sinus surgical procedures. Half the patients had CRSwNP. Patients with massive nasal polyps (>grade 2) were excluded from the study. Other patient characteristics are displayed in Table 2.

Sino-nasal outcome test-22

In the evaluation of the SNOT-22 as primary outcome, we first assessed the area under the curve (see Fig. 2). The placebo group scored better at all the time points. However, in the analysis of the area under the curve of both treatment groups, the Mann–Whitney *U*-test did not demonstrate a significant difference.

Although both treatment arms did not differ significantly, we calculated mean scores of both treatment arms and the mean of the calculated delta scores, on every time point. Complete results are demonstrated in Table 3. Statistical analysis again did not show a significant difference between the delta scores of the AZM and the placebo groups at any of the measured time points. Subgroup analysis evaluating the effects on patients with CRSwNP and asthma and a positive skin prick tests did not reveal any statistically significant differences either.

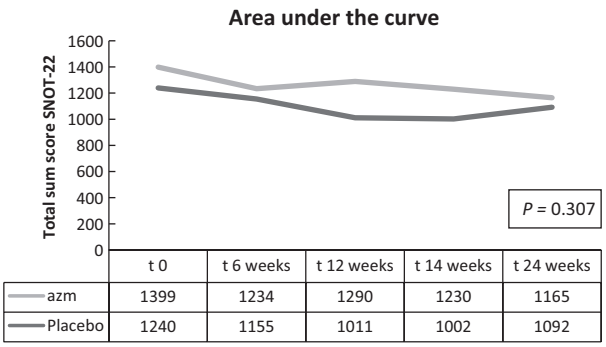

Figure 2 Area under the curve. Statistical analysis: Mann–Whitney *U*-test.

Patient response rating scale

At 6 weeks, 44% of the patients using AZM reported that they were improved or cured. In the placebo group, this percentage was 38%. At the end of the study medication at 12 weeks, 51% of the patients who used AZM improved or were cured. In the placebo group, this was 35%. At 2 weeks without study medication, patients using AZM still reported improvement/cure in 39%. In the placebo group, this was 33%. Statistical analysis, however, demonstrated no significant difference between the AZM and the placebo groups at any of these time points.

At the telephonic consultation at 12 weeks after cessation of the trial medication, Response Rating Scale data were not available for 16 patients (seven patients using AZM and nine using placebo), mostly because of loss to follow-up or incomplete documentation. In the AZM group, 50% of the residual 22 patients still reported improvement/cure, and in the placebo arm, 9% (two patients) reported that they considered themselves cured, but the rest of the patients were doing the same as before the medication or were doing worse. The difference between the AZM and the placebo groups at this telephonic consultation was significant ($P = 0.017$). Complete results are displayed in Fig. 3. Subgroup analysis evaluating patients with nasal polyps, asthma and positive skin prick test results did not reveal statistical significant differences at any of the time points between the treatment arms.

Visual analogue scale

The mean delta scores ($t_{12} - t_0$) of both treatment arms of the VAS items are presented in Table 4. All these items show a decrease (improvement), except facial pain, coughing and tooth pain in the AZM group. Facial pain was the only symptom with a significant difference between the AZM arm and the placebo arm, in favour of the placebo group. In all the other items, no difference between the treatment arms was found. The results of the most important items are also displayed in Fig. 4, demonstrating the delta scores in graphs.

Subgroup analysis for nasal polyps, asthma and positive skin prick test results was again performed and did not reveal any significant difference except for one item. In patients with a positive skin prick test, coughing did not improve. This was significantly different from the group with a negative test. We should keep in mind that this could be a result of the multiple testing.

Short Form-36

Analysing the quality of life results of the SF-36 questionnaire with the test of fixed effects, we found no statistically

Table 3 Sino-Nasal Outcome Test-22 (SNOT-22)

Mean SNOT-22 score (SD)	T_0	$T_{6\ weeks}$	$T_{12\ weeks}$	$T_{14\ weeks}$	T_{tc}
Azithromycin (AZM)	48.2 (25.3)	42.6 (25.9)	44.1 (29.4)	42.9 (28.0)	38.0 (25.6)
Placebo	40.0 (19.8)	37.3 (19.8)	32.6 (19.4)	34.2 (17.7)	38.0 (19.0)
N=	60	60	56	53	51
Mean of the delta scores (SD)		$T_{6\ weeks}$ vs T_0	$T_{12\ weeks}$ vs T_0	$T_{14\ weeks}$ vs T_0	T_{tc} vs T_0
AZM		–5.7 (15.6)	–3.6 (21.7)	–3.7 (16.7)	–8.5 (20.3)
Placebo		–2.7 (12.8)	–8.1 (16.8)	–8.9 (15.6)	–5.2 (18.9)
Mann–Whitney *U*-test		$P = 0.378$	$P = 0.192$	$P = 0.298$	$P = 0.528$

Mean SNOT-22 score (standard deviation) and mean of the delta scores (standard deviation) Statistical analysis: Mann–Whitney *U*-test on the delta scores.

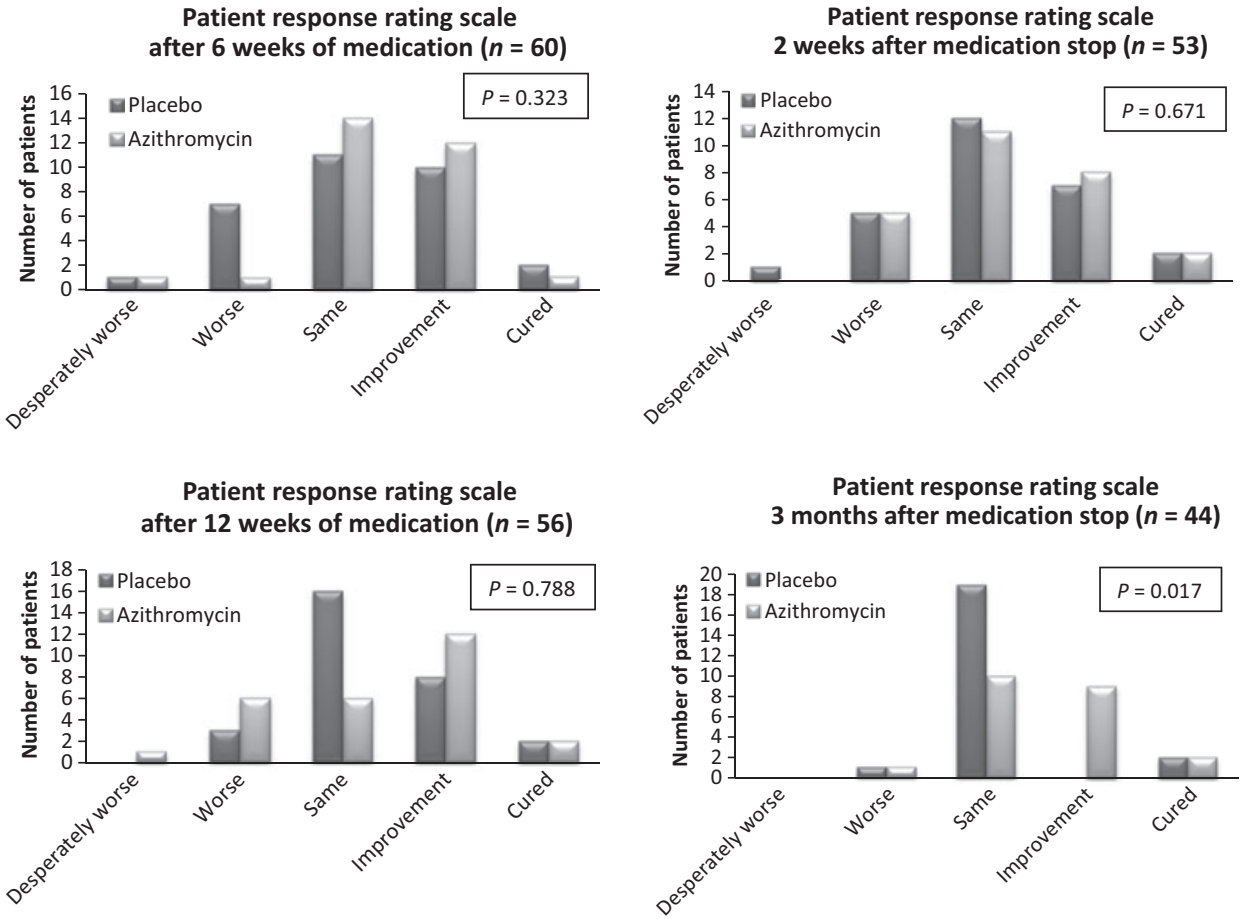

Figure 3 Patient Response Rating Scale. After 6 and 12 weeks using study medication, and 2 weeks and 3 months after medication ceased. Statistical analysis: Mann–Whitney *U*-test on the delta scores.

significant differences between the AZM arm and placebo arm, except for role emotional. However, looking at the next step in this analysis (estimates of fixed effect), we could not find any significance on any time point anymore. Analysing the results on the separate time points, again no significant difference between the two treatment arms was found, except for bodily pain (BP) at 6 weeks of using the study medication (Table 5).

Nasal endoscopy, PNIF and smell test

The items scored by rigid endoscopy included mucosal colour (left and right), mucosal swelling (inferior and middle turbinate; both sides), nasal secretions, crusts and polyps (inferior, middle meatus and ethmoid area; both sides) and postnasal drip, which make a total of 25 items. Delta scores were

Table 4 Visual Analogue Scale (VAS) delta scores

VAS score	Mean azithromycin (SD)	Mean placebo (SD)	*P*-value
Headache	−0.3 (2.7)	−0.7 (3.2)	0.825
Nasal obstruction	−1.1 (3.6)	−1.4 (2.9)	0.600
Rhinorrhea	−0.7 (3.1)	−0.7 (2.2)	0.571
Postnasal drip	−0.5 (3.3)	−1.3 (3.0)	0.441
Feeling of fullness	−0.6 (3.4)	−1.6 (3.3)	0.195
Smell reduction	−0.4 (3.5)	−0.9 (3.2)	0.192
Facial pain	0.7 (3.3)	−0.6 (2.5)	0.047*
General health	−0.3 (3.0)	−0.7 (2.6)	0.441
Tiredness	−0.5 (2.7)	−0.7 (3.0)	0.283
Coughing	0.1 (3.1)	−1.1 (2.9)	0.144
Nasal crusts	−0.3 (3.4)	−0.8 (2.5)	0.583
Nose bleeds	−0.3 (1.6)	−0.3 (1.5)	0.307
Tears	−1.0 (3.1)	−0.7 (1.9)	0.961
Tooth pain	0.3 (3.0)	−1.0 (1.9)	0.116
Nausea	−0.2 (2.5)	−0.4 (0.8)	0.668
Vomiting	−0.1 (1.7)	−0.5 (1.2)	0.452
Diarrhoea	−0.3 (2.0)	−0.5 (1.2)	0.257

Statistical analysis: Mann–Whitney *U*-test on the delta scores ($t_{12} - t_0$). *P value < 0.05 is significant.

calculated (score at the end of the treatment minus base line score). Comparing the AZM group with the placebo group, only one item showed a significant difference in the chi-square test for trend. Secretions in the left middle meatus improved more in the antibiotic group. No significant difference was found in all the other items, supporting the results of the questionnaire data. Subgroup analysis on positive skin prick tests showed no significant differences either. In the subgroup analysis on asthma, 1 of the 25 items and in the analysis on nasal polyps, 3 of the 25 items showed a significant difference in the chi-square test for trend. Of course, these results should be interpreted with caution, because of the multiple tests performed.

Delta scores were calculated for the PNIF data by subtracting the score at a measured time point from the baseline score. Measured time points included 6 weeks, at the end of the 3-month treatment period, and 2 weeks after the cessation of the study medication. No significant difference was found comparing the AZM arm with the placebo arm (see Table 6). Subgroup analysis on the presence of polyps and asthma did not show significant differences. The analysis on the positive skin prick test did only show a significant difference at 2 weeks after cessation of the medication. Patients with a positive allergic reaction did significantly worse than patients without a positive test.

At the start of the trial, the mean score of the smell test was 5.7 (maximum 12). In the AZM group, this score was five and in the placebo group 6. The smell tests were performed at the start of the medication, and at 6 and 12 weeks of medication use. On these time points, no significant difference between the two arms was found. Subgroup analysis on the presence of polyps and asthma, and a positive skin prick test or smoking did not show significant differences in any of the calculations.

Bacteriology

Nasal swabs guided by rigid endoscopy were taken from the middle meatus for microbiological examination before and after the completion of the treatment. At the start of the trial, 50 (83%) patients had a positive culture. The culture of four patients (7%) was sterile. The culture results of six patients (10%) were not available. Many cultures (60%) showed commensal nasal flora (nonpathogenic bacterial growth). Possible pathogenic species cultured included *Staphylococcus aureus*, *Streptococcus pneumonia*, *Haemophilus influenza*, *Klebsiella*, *enterobacteriaceae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*. Several fungal species were also found in some cultures, most likely due to contamination. No significant difference was found between the AZM and placebo arms for any of the species. Culture results at the start of the trial and at the end of treatment for both the AZM and placebo groups are displayed in Fig. 5. In the AZM group, a significant decrease for *S. pneumonia* ($P = 0.016$) was found.

At the start of the study medication, 3 of 50 cultures (6%) were resistant to macrolides. In two of these resistant cultures, *S. aureus* was found, one in the placebo and one in the AZM group. The third resistant culture showed *S. pneumoniae* in a patient of the AZM group. Thirty of the 50 (60%) cultures demonstrated more than one species. At the end of the course, 4 of 43 (9%) cultures were resistant to macrolides. The resistant *S. aureus* in the placebo-treated patient was again cultured. In the placebo group, two other cultures (commensals and *S. pneumoniae*) were resistant to macrolides. The fourth resistant culture, and the only one in the AZM group, was *S. pneumoniae*. Eighteen of the 43 (42%) cultures showed more than one species.

Adverse events

No serious adverse events were reported during the use of the trial medication other than mild gastrointestinal complaints, mostly mild diarrhoea. This was reported in two patients in both groups. Headache, different from rhinosinusitis-related facial pain/pressure, was reported in one patient, in each group.

Discussion

Chronic rhinosinusitis is a heterogeneous group of debilitating conditions with a collective definition based on symptom duration, nasal endoscopic observations and/or radiological findings. Despite the progress in the treatment for CRS in the last decades, there is still a subpopulation of patients with recalcitrant disease unresponsive to the conventional treatment schemes. The assumption that the mucosa and in some cases, the underlying osteitic bone are important factors in the persistence of the disease could warrant the use of long-term, low-dose antibiotics. Medical treatment is aimed not

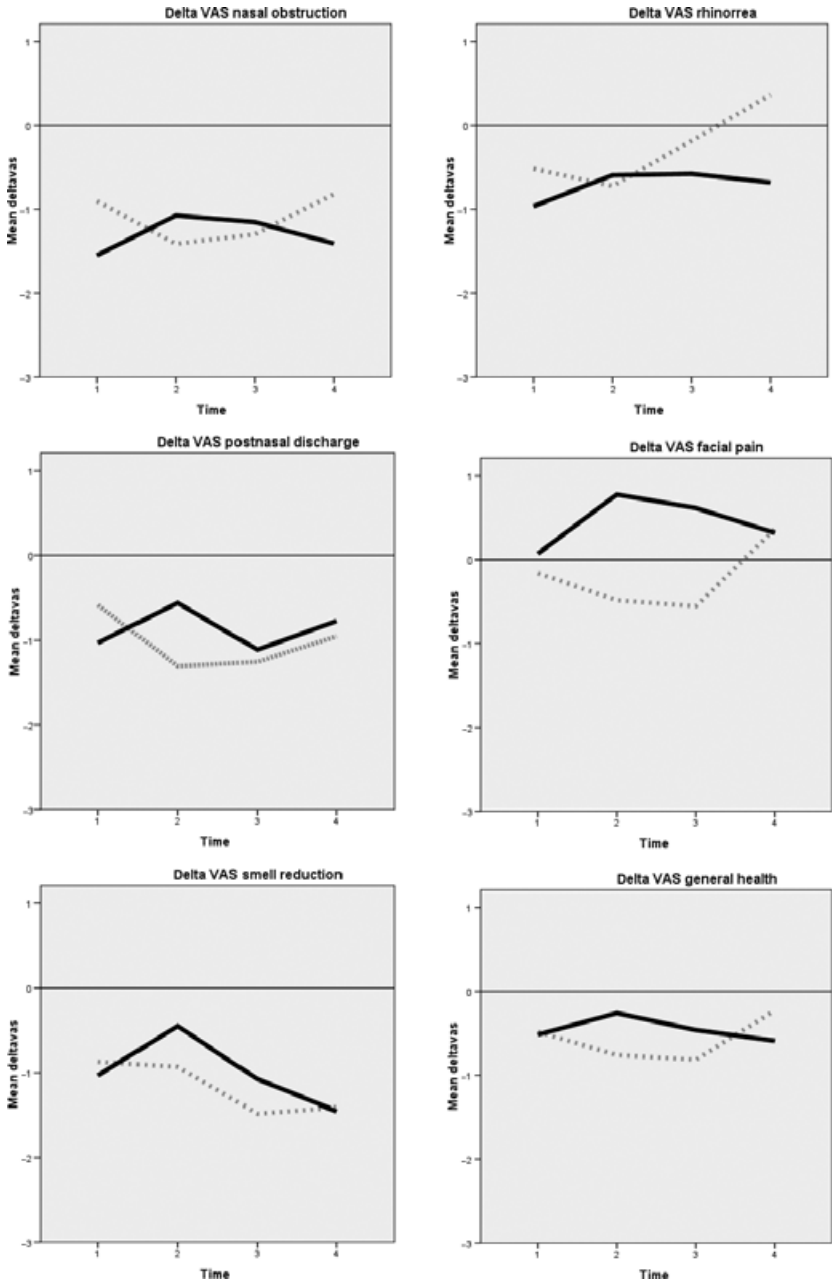

Figure 4 Visual Analogue Scale delta scores azithromycin versus placebo. Legends: grey dotted line indicates placebo and black line indicates azithromycin. Time point 1: delta score at 6 weeks, 2: delta score at 12 weeks, 3: delta score after 2 weeks without treatment, 4: delta score at telephonic consultation after 12 weeks without medication.

only at eradicating bacteria, but also at reducing inflammation, restoring ciliary function and improving aeration of the sinuses.

The efficacy of long-term, low-dose treatment with antibiotics in diffuse panbronchiolitis (DPB), a disease of unclear aetiology, characterized by chronic progressive inflammation in the respiratory bronchioles, inspired the Asians to treat CRS in the same way. A number of reports have stated that long-term, low-dose macrolide antibiotics show clinical benefit in CRS by reducing inflammation and biofilm formation and by preventing *Pseudomonas aeruginosa* colonization (9, 10, 32–35).

Besides antibacterial properties, macrolides have been shown to possess immunomodulatory properties similar to those of corticosteroids. In animal studies, macrolides have increased mucociliary transport, reduced goblet cell secretion,

Table 5 Short Form-36 (SF-36)

SF-36 Placebo versus AZM	P_{t6}	P_{t12}	P_{t14}
PF = physical functioning	0.310	0.677	0.501
RP = role physical	0.547	0.739	0.779
BP = bodily pain	0.004*	0.127	0.619
SF = social functioning	0.686	0.981	0.918
MH = mental health	0.991	0.452	0.940
RE = role emotional	0.164	0.590	0.522
VT = vitality	0.669	0.455	0.251
GH = general health	0.836	0.725	0.248
PCS = physical component score	0.110	0.304	0.581
MCS = mental component score	0.824	0.686	0.988

Calculated *P*-values, comparing the azithromycin (AZM) with the placebo group at time points after 6 and 12 weeks of medication and after 2 weeks after the end of the study medication course. Statistical analysis: Mixed-model analysis. *P value < 0.05 is significant.

Table 6 Peak nasal inspiratory flow delta scores (SD)

	T_6 AZM	T_6 Placebo	T_{12} AZM	T_{12} Placebo	T_{14} AZM	T_{14} Placebo
Mean	5.3	−4.7	7.4	−0.3	−0.2	4.3
SD	31.5	22.3	42.0	33.9	32.5	31.0
P-value	0.156		0.322		0.872	

Statistical analysis: Mann–Whitney *U*-test.
AZM, azithromycin.

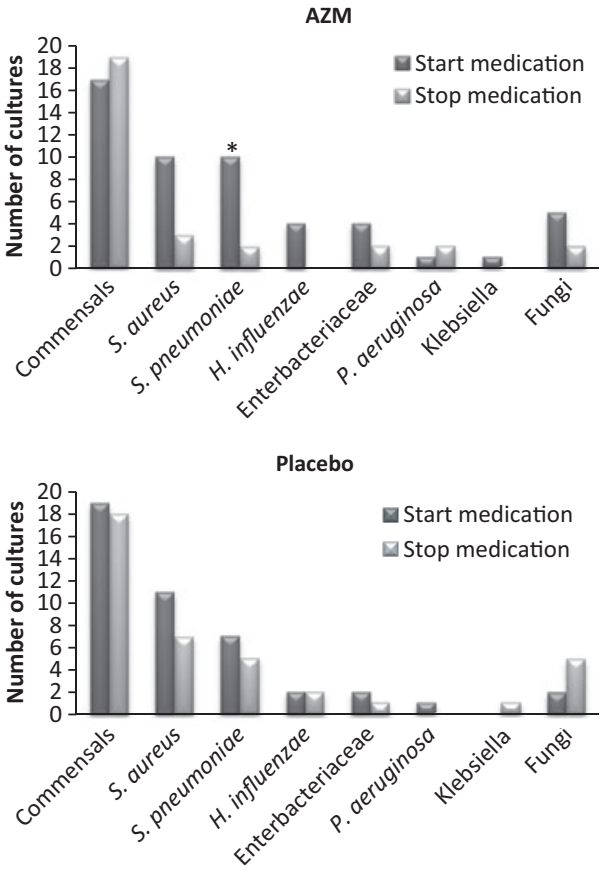

Figure 5 Bacteriology at baseline and after completion of the study medication. Statistical analysis: McNemar test.

accelerated apoptosis of neutrophils, reduced expression of cell surface adhesion molecules, altered structure and function of biofilm, and macrolides have shown to decrease the levels of IL-5, IL-6, IL-8, GM-CSF, TGF-β and TNF-α (12, 32–34, 36–39). There is also evidence *in vitro* showing that macrolides reduce the virulence and tissue damage caused by chronic bacterial colonization without eradicating the bacteria (40). However, to date, the *in vitro* results could not be demonstrated *in vivo* in many cases. Therefore, it remains to be established whether these findings are clinically relevant.

As a consequence of the promising data in the literature, long-term, low-dose antibiotics are already been administered to patients with recalcitrant CRS in an increasing number of outpatient clinics, despite the lack of hard clinical evidence (41). It is also included as a treatment choice in the management of CRS without nasal polyps in the EP^{3}OS document (1). As mentioned earlier, the MACS trial is only the second randomized, placebo-controlled trial on macrolides in the treatment for CRS.

In summary, the MACS trial did not demonstrate benefits for the CRS patients treated with AZM over placebo: not in the results of four different questionnaires, nor in the multiple items evaluated during rigid nasal endoscopy, nor in the results of PNIF, smell tests and microbial evaluation.

A guarded exception could perhaps be made for the results of the Patient Response Rating Scale. There was no significant difference between the results of both arms, during, at the end and after 2 weeks after cessation of the study medication. However, at the telephonic consultation, 3 months after the end of the study medication, there were significantly better results in the AZM group compared with the placebo group. However, 16 patients were lost to follow-up, possibly as a result of selection bias. In the VAS results, we found a significant difference for facial pain. Surprisingly, the placebo group did better than the group treated with antibiotics. We are aware of the fact that we performed an extended number of tests analysing the data. Owing to this multiple testing, an occasionally significant result is more likely to occur.

In Amsterdam alone, 59 suitable patients were identified and asked to participate in the MACS trial. Only 32 (54%) of these Dutch patients approved participation, mainly because they did not want to risk the chance of a placebo treatment. This percentage of suitable patients in the other centres is not known. Owing to this difficulty of enrolment, the MACS trial period took almost 3 years.

Our results are in some degree comparable with the data of the study by Wallwork (14). Unfortunately in our study, we did not analyse total IgE levels in a majority of patients, so a subgroup analysis of the patients with low IgE level was not possible. However, the subanalysis performed on skin prick test results did not demonstrate data with significant

relevance. This study does not support the data from the study by Ragab (13). The difference between Wallwork's investigation and the MACS trial compared with the Ragab study is the inclusion of a placebo group. We cannot exclude that in the Ragab study, a placebo group would have had a positive result too. However, the reduction in SNOT-20 in the Ragab study was definitely larger than in the Wallwork and MACS study for which we do not have an explanation.

Bacteriology did not show significant differences between the AZM and the placebo groups either, although in the AZM group reduction was achieved by the study medication, which was significant for *S. pneumoniae*. One could suggest that even at the present low-dose, microbial flora seems to be modified, although clinical impact was not demonstrated. In long-term, low-dose administration of antibiotics, there is often a discussion between the clinician and microbiologist regarding the possible induction of resistant of microorganisms. In our opinion, the resistant strain demonstrated in the study was not inducted by the study medication but more likely to be the result of selective pressure of long-term, low-dose antibiotics.

Multiple comments can be made on the drawbacks of this double-blinded, randomized, placebo-controlled study. However, before we discuss them, we would like to stress the recalcitrant nature of CRS studied in this population. All of the participating patients had suffered from CRS for many years and were unresponsive to conventional treatment regimes, and the majority had undergone repeated sinus surgery. A substantial number of the patients suffered from mild nasal polyps and/or had a positive skin prick test, indicating important comorbidity. It could be possible that in a better-selected subgroup of patients with CRS, without nasal polyps for example, results would be more promising. This would fit better with the findings of daily practice where macrolides seem to work in some people. The problem could be related to the definition of the population.

The appropriate dosage of AZM could also be a point of discussion. It is generally accepted when using prolonged courses of antibiotics to start with the conventional dose used to treat an acute infection. Thereafter, half of this dose is given for weeks or months. In the literature, there are reports of the beneficial effect of AZM with a comparable dosage used in this study for the treatment for recurrent acute otitis media in children, for prophylaxis against agents causing acute respiratory disease in the army (42) and for prostate infection caused by *Chlamidia trachomatis*, to name but a few (22, 43, 44). However, the once weekly dose of 500 mg appears not to be effective in this study, as a possible result of under-dosage for the treatment for CRS. In trials on prolonged macrolide use in cystic fibrosis patients, clinical significant effects are demonstrated using higher-dosage schemes of between 1200 mg weekly and 250 mg daily during 6 months (44). In normal ENT practice, especially in tertiary referral centres for recalcitrant CRS, often the long-term antibiotic course is prolonged until a stable situation has been achieved. This can sometimes be a significantly longer period of time than the arbitrary chosen time window of 3 months used in this trial. It could therefore be that the period of treatment has been too short for AZM in the present dosage. Unfortunately, we did not control tissue or serum levels to evaluate the minimal inhibiting concentration (MIC). For the evaluation of a prolonged course of antibiotics, the follow-up was relatively short: 2 weeks and 3 months after cessation of the study medication. On the other hand, it is unlikely that there would be a beneficial effect caused by AZM, 3 months after medication stop, if there is no significant improvement demonstrable during the course itself. Under-powering of the study could also be a relevant reason that has been mentioned earlier. Patients were hard to recruit, and most of them continuously demanded next steps in the treatment process. As a result of the multicentre set-up of the MACS trial, there is a risk of an interobserver bias. Patients were seen by different rhinologists at different centres, in different countries. Although there is frequent communication between these rhinologists and they work according to the latest European treatment schemes, this risk cannot be ruled out.

To further evaluate the usefulness of a long-term, low-dose macrolides in the treatment for recalcitrant CRS much work is still required. The existence of different subgroups within the CRS population seems to surface again. The treatment might be useful, in an as yet unidentified subpopulation, rather than in every patient with CRS. Future research should focus on the identification of characteristics of such subpopulations, and poor prognostic factors should be recognized. *Suzuki* et al. reported that elevated IgE levels and substantial eosinophilia in smears, tissue or blood were poor prognostic factors (45). In our population, the total IgE level was found to be available in a too small number of patients to further evaluate this element. However, 32% of the patients had a positive skin prick test, which makes atopy a substantial factor in this population. The presence of nasal polyps also has been reported as being unfavourable for the efficacy of long-term, low-dose antibiotic treatment (12, 13, 46–48).

This study has demonstrated that AZM at this dosage is not an option in the battle against recalcitrant CRS. Other members of the macrolide family, other dosage schemes and different treatment periods have to be evaluated to further define the role of long-term, low-dose macrolides in the treatment for recalcitrant CRS.

Acknowledgments

First of all the authors thank all the patients who were willing to participate in the MACS trial. Without them, this research project would have been impossible. We also thank PLIVA for kindly providing the study medication, without any costs. Last but not the least, we thank C. M. C. McPharland for her work in the set-up of the MACS trial, and N. van Geloven and P. T. Nieuwkerk for their assistance in the statistical analysis.

Author's contributions

W. J. Videler, V. J. Lund, and W. J. Fokkens designed the study, collected the data, and involved in literature search,

data interpretation and writing. L. Badia, R. J. Harvey, S. Gane, C. Georgalas, F. W. van der Meulen, D. J. Menger, M. T. Lehtonen, S. K. Toppila-Salmi, S. I. Vento, M. Hytönen and P. W. Hellings collected data and commented on the writing. L. Kalogjera designed the study, involved in data collection and data interpretation, and commented on the writing. G. Scadding designed the study, involved in data collection and commented on the writing. J. Mullol designed the study, collected data, searched literature and commented on the writing.

Funding

The Azitromycin and placebo used in this study was kindly provided by PLIVA HRVATSKA d.o.o., Zagreb, Croatia.

Conflict of interest

None

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