

# Azithromycin for chronic eosinophilic rhinosinusitis with nasal polyp: a placebo-controlled trial\*

Isamara Simas de Oliveira<sup>1</sup>, Alessandro Fernandes Guimaraes<sup>2</sup>, Gabriela Rafaela Arantes Pêgas<sup>3</sup>, Carla Jorge Machado<sup>4</sup>, Geovanni Dantas Cassali<sup>5</sup>, Paulo Fernando Tormin Borges Crosara<sup>6</sup>, Flávio Barbosa Nunes<sup>6</sup>, Helena Maria Gonçalves Becker<sup>6</sup>, Roberto Eustáquio Santos Guimarães<sup>6</sup>

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<sup>1</sup> Post Graduate Program in Surgery and Ophthalmology, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil

<sup>2</sup> Resident Physician of Craniomaxillofacial Surgery of the Hospital das Clínicas, UFMG, Belo Horizonte, Minas Gerais, Brazil

<sup>3</sup> Undergraduate student of the Department of General Pathology, UFMG, Belo Horizonte, Minas Gerais, Brazil

<sup>4</sup> Department of Preventive and Social Medicine, UFMG, Belo Horizonte, Minas Gerais, Brazil

<sup>5</sup> Department of General Pathology, UFMG, Belo Horizonte, Minas Gerais, Brazil

<sup>6</sup> Department of Ophthalmology and Otolaryngology, UFMG, Belo Horizonte, Minas Gerais, Brazil

## Abstract

**Background:** Chronic eosinophilic rhinosinusitis with nasal polyps (CRSwNP eosinophilic) is characterised by the formation of benign and bilateral nasal polyps. We aimed to compare the effectiveness of azithromycin as an immunomodulator with the use of a placebo in patients presenting with CRSwNP concomitant with asthma and aspirin intolerance after 3 months of treatment and at a 1-year follow-up.

**Methodology:** We performed a randomised, double-blind, placebo-controlled trial. Patients received 500 mg azithromycin orally three times/week for 12 weeks. Improvement was evaluated by staging, the Sino-Nasal Outcome Test (SNOT-22), and nasal polyp biopsy. Data collected at pretreatment and 3 months posttreatment were compared. Quality of life was evaluated at the 1-year follow-up.

**Results:** Twenty-seven and 21 patients were treated with azithromycin and a placebo, respectively. The medication was well tolerated overall. Twenty patients (74%) in the azithromycin group and three patients (14%) in the placebo group were not referred for surgery at the end of the 3-month treatment. Regarding subjective improvement, there was a median decrease only in the azithromycin group, and the between-group difference was significant. SNOT-22 improvement was maintained in the azithromycin group at the 1-year follow-up.

**Conclusions:** Azithromycin could be considered a therapeutic option for patients presenting with CRSwNP concomitant with asthma and aspirin intolerance.

**Key words:** aspirin, azithromycin, endoscopy, eosinophils, nasal polyposis

## Introduction

Chronic eosinophilic rhinosinusitis with nasal polyps (CRSwNP), which belongs to the heterogeneous group of CRSwNPs, is the most common nasal polyposis disease and accounts for 85%–90% of polyposis cases<sup>(1–5)</sup>. When CRSwNP is concomitant with asthma and aspirin intolerance, it is known as nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease

(N-ERD)<sup>(6)</sup>.

Corticosteroids are considered the main therapeutic option for CRSwNP<sup>(7,8)</sup>, as they suppress the inflammatory process. However, the systemic use of these drugs presents a wide range of side effects, thereby prohibiting their prolonged use. Nasal endoscopic surgery could be a therapeutic option in cases refractory to clinical treatment<sup>(9)</sup>. Nevertheless, recurrences of NPs

are frequent, even after the use of broad surgical approaches, and may reach rates of 50% in cases of massive NPs<sup>(10)</sup>. The monoclonal anti-IgE antibody omalizumab can effectively relieve nasal symptoms in patients with N-ERD, but there is no evidence that this antibody prevents polyp recurrence after surgery<sup>(11)</sup>. Although aspirin treatment after desensitisation (ATAD) may improve CRSwNP and the course of asthma in patients with N-ERD, patients should be carefully selected for ATAD and monitored during treatment to assess treatment efficacy and to reduce the prevalence of adverse effects associated with aspirin intake<sup>(12)</sup>. The use of macrolides as immunomodulators is important in this context<sup>(13,14)</sup>. In our previous work, we used azithromycin<sup>(15)</sup>; the study design precluded definite conclusions on medication efficacy, but promising effects were observed in patients with extensive nasal polyposis.

The present study evaluated the effect of azithromycin in a homogeneous group of patients with CRSwNP with asthma and aspirin intolerance in comparison with a placebo. Comparisons were also performed to evaluate changes in the scores on the Sino-Nasal Outcome Test (SNOT-22), changes in the staging of polyposis<sup>(16,17)</sup>, inflammatory infiltration<sup>(18)</sup>, and the eosinophil count between pretreatment and posttreatment. Additionally, patients were followed up for 1 year after the intervention and re-examined with the SNOT-22. To the best of our knowledge, this work is the first to evaluate a specific and homogeneous group of chronic rhinosinusitis patients (i.e., patients with N-ERD). In addition, follow-up was performed for a period of 1 year.

## Materials and methods

The study was approved by the ethics and research committee of the Federal University of Minas Gerais (UFMG) (CAAE-05599012.3.0000.5149, approval no: 2.361.591). As this was a clinical trial, the project was registered in the Brazilian Registry of Clinical Trials under the number RBR-9pqqpb, UTN number: U1111-1201-8926. All patients agreed to participate and provided signed informed consent after receiving a thorough explanation of the study.

The minimum sample size required for the study was estimated using a significance level of 5% ( $\alpha = 0.05$ ) and a statistical power of 80% ( $\beta = 0.2$ ) to detect a difference of 14 points on the SNOT-22<sup>(16)</sup> (for the SNOT validated for Portuguese, this difference would be considered significant). Assuming a standard deviation lower than 28, the minimum estimated sample size was 21 in each group and thus 42 in total. The initial plan was to collect data from 60 patients (to allow for attrition); 30 individuals group were treated with 500 mg azithromycin, and 30 patients were treated with a standardised placebo. Due to administrative reasons at the hospital, patient recruitment was suspended before 60 patients could be included. The appointment of new patients was suspended, and it was not possible to continue the inclusion. As there was a satisfactory sample size (at least 21

patients in each group), this did not affect our project. Randomisation was performed using a freely available online random number generator at <https://www.random.org/sequences><sup>(19)</sup>. The designated pharmacist helped to handle placebo treatments. The vials were assigned numbers and randomised. We included patients who were at least 18 years old, had CRSwNP with asthma and aspirin intolerance, had a percentage of eosinophils > 40% in the polyp biopsy specimen, did not exhibit evidence of active nasal infection (e.g., purulent secretion in the nasal cavity) in the clinical and endoscopic examinations, had previously undergone unsuccessful standard clinical treatment (oral and topical corticosteroids), and had received a formal recommendation for endoscopic nasal surgery. Patients were excluded if they had noneosinophilic polyp types, such as cystic fibrosis, Kartagener syndrome, antrochoanal polyps, and/or CRSwNP with active infection; CRSwNP without asthma or aspirin intolerance; corticosteroid/antihistamine and short-term antibiotic use within 15 and 30 days before the beginning of the study, respectively; established cardiovascular and/or hepatic disease; or electrocardiographic changes (e.g., prolonged QT interval).

The patients had an established clinical-endoscopic-radiological-histopathological CRSwNP diagnosis<sup>(4)</sup>, asthma, and a clear history of multiple reactions developed within 1–2 hours of NSAID ingestion, manifesting as upper and/or lower airway symptoms<sup>(20)</sup>. All patients had already been unsuccessfully treated with optimised standard drug therapy (e.g., oral or topical corticosteroids) and thus had an indication for salvage nasosinus endoscopic surgery. The study was conducted at the São Geraldo Hospital, an annex of the Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG). Patients generally arrived at the outpatient clinic without the use of any oral or topical medication to control their CRSwNP symptoms, as the previous unsatisfactory response discouraged them from continuing such treatment. A researcher (I.S.O.) recruited the participants from the population of patients who arrived at the clinic.

## General design

This was a randomised, double-blind, placebo-controlled trial involving patients with CRSwNP, asthma, and aspirin intolerance. We compared clinical responses before and after treatment in each group and between groups.

The study began with a complete otolaryngologic evaluation, staging<sup>(17)</sup>, and polyp biopsy. After inducing nasal cavity anaesthesia with cotton soaked in 2% neotonocaine, polyps measuring 5 × 2 mm in size were removed using EXPLORENT (Olympus America Inc., Center Valley, PA, USA) forceps, avoiding maceration of the tissue. Complementary tests were requested, including an electrocardiogram, complete blood cell count, and hepatic

function tests. The latter were requested because azithromycin is metabolized in the liver.

The patients were assisted by one of the authors (I.S.O.) while completing the SNOT-22<sup>(16)</sup> and Visual Analogue Scale (VAS). The VAS is described as a gravity characterisation tool according to the European Rhinosinusitis Consensus<sup>(4)</sup>.

Subsequently, a 500-mg coated tablet of azithromycin dihydrate (AZI®) (EMS S/A, Hortolândia, São Paulo, Brazil) or a standardised placebo was orally administered at a dosage of one tablet (500 mg) three times/week (Monday, Wednesday, and Friday) for 12 weeks<sup>(21-25)</sup>. The medication was donated by the Rhinology Out-patient Clinic, Hospital das Clínicas da UFMG (HC-UFMG). The drug and placebo vials were identical and randomly numbered using a website providing a random number generator (<https://www.random.org/>) by the designated pharmacist for the placebo design, who revealed which vials contained AZI® only at the end of the study. Thus, the researcher who registered the patients and collected the data, the patients, and the pathologist were all blinded to treatment allocation. Only the pharmacist had access to the groups.

In week 13, the patients returned to the outpatient clinic for follow-up clinical and endoscopic evaluation and staging, a new biopsy of the nasal polyp was performed, and the SNOT-22 and VAS were completed. At that point, the patients were also asked about the presence of adverse effects, the appropriate use of the medication, and possible delays or omissions of doses. All patients reported the complete and correct use of the medication provided. They also delivered the empty vials and the use log.

### Variables analysed

**Subjective improvement.** During their return to the outpatient clinic at week 13, the patients were asked about improvements in their symptoms. They were also interviewed using the VAS to define symptom discomfort and the surgical indication at that time.

**Quality-of-life questionnaire.** The SNOT-22 was translated, validated, and adapted to the Portuguese language (Brazil) in 2011<sup>(16)</sup>. The instrument consists of 22 questions and/or symptoms that can be scored by the patients on a scale ranging from 0 (no problem) to 5 (the worst possible problem) based on their symptom experience in the past 2 weeks. The normality limit for the Brazilian SNOT-22 is 10 points, and a variation of >14 points among SNOT-22 scores of the same patient is considered significant. The patients completed the SNOT-22 before treatment, at week 13, and at 1 year after treatment.

**Staging.** Although several polyp-staging methods have been described in the literature, there is no universal consensus on the ideal method. The staging method chosen in the present study has been used in the Otolaryngology Service of HC-UFMG for several years. The method consists of three-dimensional

Table 1. Three dimensional staging<sup>(17)</sup>.

| Staging         | Characteristics   |
|-----------------|---|
| Horizontal      |   |
| H0              | No polyps   |
| H1              | Polyps restricted to the middle meatus  |
| H2              | Polyps expand beyond the middle meatus, without touching the nasal septum                                 |
| HT              | Polyps expand beyond the middle meatus and touching the septum  |
| Vertical        |   |
| V0              | No polyps   |
| V1              | Polyps in the middle meatus only  |
| V1              | Polyps extending inferiorly to the middle meatus, going beyond the upper border of the inferior turbinate |
| VS              | Polyps extending superiorly to the middle meatus, between the septum and the middle turbinate             |
| VT              | Polyps occupying the entire vertical aspect of the nasal cavity   |
| Anteroposterior |   |
| P0              | No polyps   |
| P1              | Polyps in the middle meatus only  |
| PA              | Polyps extending anteriorly to the middle meatus, reaching the head of the inferior turbinate             |
| PP              | Polyps extending posterior to the middle meatus, reaching the tail of the inferior and middle turbinate   |
| PT              | Polyps occupying the entire anteroposterior aspect of the nasal cavity                                    |

staging, which has the advantage of identifying polyp locations in three-dimensional space, and classifies polyp locations in regions other than the middle meatus<sup>(15,17)</sup>. The method is exclusively based on nasal endoscopy (nasofibroscopy). Each nasal cavity was staged separately (Table 1).

**Histologic evaluation.** The slides were stained with haematoxylin and eosin and evaluated by an Olympus BX-40 microscope (X10 ocular and X40 objective) (Olympus America Inc.). The images were captured with a spot insight colour microcamera (Diagnostic Instruments, Inc., Sterling Heights, MI, USA), adapted to the microscope using the SPOT Basic 3.4.5 software (Diagnostic Instruments, Inc.), and analysed using Corel Draw version 7.468 (Corel Corporation, Ottawa, Canada). The cellularity was analysed by exploring five fields of the optical microscope with 400× magnification, as suggested by Ingels et al.<sup>(26)</sup>. The inflammatory infiltration was semiquantitatively evaluated following well-defined criteria<sup>(15,18)</sup> and classified according to its distribution and intensity. The distribution was characterised as focal, multifocal, or diffuse depending on the presence of one to three or more than three inflammatory foci and uniformly distributed inflammatory cells. The inflammatory reaction intensity was

Table 2. Study group series (sample homogeneity).

| Variables                                  | Description/Categories | Placebo Group | Azithromycin Group | P value |
|--|------------------------|---------------|--------------------|---------|
| Gender                                     | Female (n; %)          | 14 (66.7)     | 13 (48.2)          | 0.020   |
|  | Male (n; %)            | 7 (33.3)      | 14 (51.9)          |         |
| Age  | Mean (SD)              | 43.8 (10.4)   | 51.8 (13.,1)       | 0.0275  |
|  | Median (IIQ)           | 43 (14)       | 53 (18)            | 0.0282  |
| VAS* pre                                   | Mean (SD)              | 8.67 (1.46)   | 8.63 (2.13)        | 0.946   |
|  | Median (IIQ)           | 9 (2)         | 10 (2)             | 0.520   |
| SNOT-22** pre                              | Mean (SD)              | 65.8 (21.7)   | 66.3 (22.6)        | 0.945   |
|  | Median (IIQ)           | 70 (34)       | 62 (23)            | 0.909   |
| Staging pre                                | Mean (SD)              | 13.9 (2.9)    | 13.6 (3.3)         | 0.771   |
|  | Median (IIQ)           | 14 (5)        | 14 (5)             | 0.857   |
| Inflammatory infiltrate pre (Distribution) | Multifocal (n; %)      | 2 (9.5)       | 5 (18.5)           | 0.445   |
|  | Diffuse (n; %)         | 19 (90.5)     | 22 (81.5)          |         |
| Inflammatory infiltrate pre (Intensity)    | Discrete (n; %)        | 7 (33.3)      | 10 (37.0)          | 0.174   |
|  | Moderate (n; %)        | 7 (33.3)      | 14 (51.9)          |         |
|  | Intense (n; %)         | 7 (33.3)      | 3 (11.1)           |         |
| Eosinophil count pre                       | Mean (SD)              | 101.8 (72.9)  | 96.9 (67.6)        | 0.826   |
|  | Median (IIQ)           | 111.75(130.0) | 96.8 (128.7)       | 0.980   |
| Mast cell count pre                        | Mean (SD)              | 4.6 (1.8)     | 4.0 (2.3)          | 0.349   |
|  | Median (IIQ)           | 5.6 (2.2)     | 3.2 (4.2)          | 0.246   |

n = absolute number; SD = standard deviation; IIQ = interquartile range; \*VAS = visual analogic scale; \*\* SNOT-22 = Quality of life questionnaire SNOT-22

categorised into three subgroups based on the morphologic analysis of the total inflammatory infiltration: mild (+), moderate (++), and intense (+++).

For eosinophil counting, the same five fields captured using a 40x objective lens were used. The absolute number of eosinophils was counted using ImageJ (US National Institutes of Health, Bethesda, MD, USA).

All samples were analysed by an experienced pathologist blinded to the study procedures (G.D.C).

### Statistical analysis

Absolute numbers and percentages were obtained pre- and postintervention. Regarding continuous variables, the mean, median, standard deviation, interquartile range, and minimum and maximum distribution values were calculated.

The following variables were also compared in the same group pre- and postintervention: the VAS and SNOT-22 scores, staging, inflammatory infiltration, eosinophil count, and mast cell count. Sex, age groups, and inflammatory infiltration were compared using the nonparametric Wilcoxon test for dependent samples (paired). For age, VAS and SNOT-22 scores, staging, eosinophil count, and mast cell count, the mean and median values were compared using parametric Student's t-tests for paired samples and the non-parametric Wilcoxon test for dependent samples.

Differences in the same variables between the azithromycin and placebo groups were compared using the parametric Student t-test and the non-parametric Wilcoxon test for independent and dependent samples, respectively.

For the SNOT-22, the preintervention, postintervention, and 1-year follow-up scores were compared by two-by-two comparisons (preintervention/postintervention and 1-year follow-up). For all comparisons, the significance level was set at 5% ( $p < 0.05$ ).

### Results

During a 3-year period (March 2015–March 2018), we evaluated the cases of 59 patients who were diagnosed with CRSwNP, asthma, aspirin intolerance, and had indications for surgical treatment. Four patients refused the preoperative use of the medication, one patient had already undergone recent surgery, and six patients had no visible polyps on clinical examination (no biopsy possible). Thus, 48 patients completed the study (mean age, 48.29 [range, 23–74] years), including 27 and 21 patients in the azithromycin and placebo groups, respectively.

They were referred by the public health system to receive surgical treatment in the Tertiary Hospital of the UFMG (HC-UFMG). There were no significant differences in sex between the groups ( $p = 0.199$ ). Regarding age, there was a difference, as the parti-

Table 3. Results before, after 3 months and after 12 months of treatment in SNOT-22 evaluation.

| SNOT-22            | Categories   | Pre         | Post 3 months | Post 1 year | P value |
|--------------------|--------------|-------------|---------------|-------------|---------|
| Placebo Group      | Mean (SD)    | 65.8 (21.7) |               | 53.4 (24.1) | 0.170   |
|                    | Median (IIQ) | 70 (34)     |               | 50.5 (42)   | 0.424   |
| Azithromycin Group | Mean (SD)    | 66.3 (22.6) |               | 44.9 (26.7) | <0.001  |
|                    | Median (IIQ) | 63 (33)     |               | 44 (39)     | <0.001  |
| Placebo Group      | Mean (SD)    |             | 62.5 (20.9)   | 53.4 (24.1) | 0.308   |
|                    | Median (IIQ) |             | 62 (34)       | 50.5 (42)   | 0.791   |
| Azithromycin Group | Mean (SD)    |             | 49.2 (23.7)   | 44.9 (26.7) | 0.555   |
|                    | Median (IIQ) |             | 47 (35)       | 44 (39)     | 0.405   |

SD = standard deviation; IIQ = interquilitic range. Note: no statistical significant differences were found between placebo and azithrocymin within pre and post groups ( $p > 0.05$ ), but SNOT-22 post 3 months of treatment ( $p = 0.049$ ).

Participants in the azithromycin group were approximately 8 to 10 years older (mean and median) than those in the placebo group. Regarding the remaining variables, the groups were homogeneous at baseline, with no significant difference regarding the VAS ( $p = 0.946$ ) and SNOT-22 ( $p = 0.945$ ) scores, staging ( $p = 0.771$ ), inflammatory infiltration ( $p = 0.445$  and  $p = 0.174$ ), or eosinophil count ( $p = 0.826$ ) (Table 2).

**Subjective improvement**

At the end of treatment, 20 patients from the azithromycin group (74%) reported good symptom control and chose not to undergo surgical treatment, while in the placebo group, only three patients (14%) were not referred for surgery ( $p < 0.01$ ). All patients were clinically followed up at the Rhinology Outpatient Clinic of the Hospital São Geraldo. A flow chart describing the

patient inclusion and treatment processes is shown in Figure 1. There were significant differences between the pre- and post-treatment mean VAS scores in the placebo group ( $p = 0.038$ ). In the azithromycin group, there was a decrease in the mean and median VAS scores ( $p < 0.001$  in both measurements).

**Quality-of-life questionnaire**

All patients had a SNOT-22 score higher than 10 points at the beginning of the study. There was a significant decrease only in the azithromycin group ( $p < 0.001$ ), with a mean reduction of 17 points, while the placebo group only showed a 3.3-point reduction. Sixteen patients in the azithromycin group had a high (higher than 14 points) reduction (59.25%), while such a reduction was observed only in four patients in the placebo group (19.0%) (Table 3).

**Staging**

Although a reduction in staging was observed in both groups, the reduction was found to be significant only in the azithromycin group ( $p < 0.001$ ). Although the medians were the same in both groups, it was observed that after treatment, staging was concentrated at lower values compared to pretreatment (see minimum and maximum values); the nonparametric Wilcoxon test, which compares the whole distribution, revealed a significant difference between the groups (Table 4).

**Histological evaluation**

There was loss of material in two and three individuals from the placebo and azithromycin groups, respectively; these individuals were excluded from the analysis. There was no difference between the pre- and posttreatment findings in the evaluation of inflammatory infiltration. Regarding the distribution and intensity, the slides were very homogeneous in the pre-/postintervention and between-group comparisons. Moreover, the distribution was classified as multifocal or

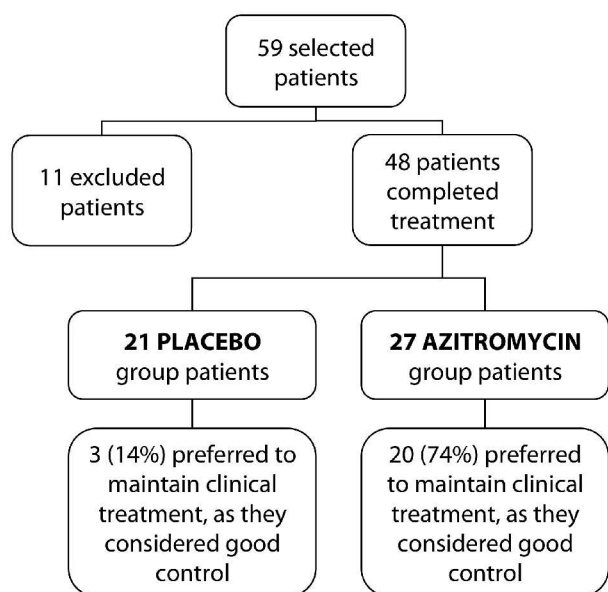


Figure 1. Casuistic diagram of the present study.

Table 4. Results pre and post 3 months in the three-dimensional staging evaluation of polyps.

| Staging            | Description  | Pre        | Post       | P value |
|--------------------|--------------|------------|------------|---------|
| Placebo Group      | Mean (SD)    | 13.9 (2.9) | 12.5 (4.6) | 0.034   |
|                    | Median (IQR) | 14 (5)     | 14 (5)     | 0.065   |
| Azithromycin Group | Mean (SD)    | 13.6 (3.3) | 11.5 (4.6) | <0.001  |
|                    | Median (IQR) | 14 (5)     | 14 (7)     | <0.001  |

SD = standard deviation; IQR = interquartile range; Note: no statistical significant differences were found between placebo and azithromycin within pre and post groups ( $p > 0.05$ ).

diffuse.

The eosinophil count in the azithromycin group was lower at posttreatment than at pretreatment. Significant pre-/postintervention differences in the mean ( $p = 0.046$ ) and median values ( $p = 0.017$ ) were observed in the treatment group; there were no significant pre-/postintervention differences in the placebo group ( $p = 0.726$  and  $p = 0.453$ , respectively) (Table 5). In general, the drug was well tolerated by the patients. Only one patient in the azithromycin group complained of mild diarrhoea, but there was no need to discontinue the medication. In the placebo group, there were two patients with dyspeptic complaints (heartburn/burning) and one with tachycardia (no changes observed on electrocardiography). These patients reported complaints at the week 13 follow up, but no patients discontinued the medication. Other patients reported no side effects even when questioned directly. There was no significant difference in the occurrence of side effects between the groups ( $p = 0.306$ ).

### Follow-up

After 1 year, the patients were evaluated again, and a new SNOT-22 was completed (in person or via phone call). Four and seven patients from the azithromycin and placebo groups, respectively, underwent surgery, and their SNOT-22 scores were not considered because of the new intervention. For the remaining patients, there was still a significant difference between pretreatment scores and 1-year follow-up scores on the SNOT-22 in the azithromycin group (Table 3).

### Discussion

The present study evaluated the treatment response in a homogeneous group of patients with CRSwNP with asthma and aspirin intolerance who were treated with azithromycin dihydrate (AZI®).

When the age (mean and median) was evaluated, the azithromycin group was found to be older. This difference could potentially compromise the findings, considering that we examined a

Table 5. Pre and post 3 months treatment results on eosinophils count in biopsies.

| Variable           | Categories   | Pre         | Post        | P value |
|--------------------|--------------|-------------|-------------|---------|
| Eosinophils        |              |             |             |         |
| Placebo Group      | Mean (SD)    | 101.8(69.4) | 92.9 (65.4) | 0.736   |
|                    | Median (IQR) | 104 (130)   | 59 (76)     | 0.453   |
| Azithromycin Group | Mean (SD)    | 96.9 (67.6) | 67.2 (63.5) | 0.046   |
|                    | Median (IQR) | 91 (135)    | 40 (81)     | 0.017   |

SD = standard deviation; IQR = interquartile range; Note: no statistical significant differences were found between placebo and azithromycin within pre and post groups ( $p > 0.05$ ).

chronic disease that may worsen over the years (longer disease duration, greater likelihood of sinus involvement). However, this was not the case, and for all the variables analysed (including polyposis staging), the groups were homogeneous at the beginning of the study; therefore, the age difference was not a limitation of this study.

All participants had been referred to the Rhinology Outpatient Clinic for nasal endoscopic surgery as salvage treatment. Moreover, they had previously undergone standard treatment for CRSwNP without satisfactory results and were therefore referred for surgery. Thus, it is an extremely relevant outcome that, at the end of treatment, 74% of patients in the azithromycin group chose not to undergo surgical treatment because they considered that they had good symptomatologic control of the disease. Conversely, in the placebo group, only 14% of patients chose not to undergo surgery.

Furthermore, in the azithromycin group, there was clinical improvement in staging and quality of life (evaluated based on the VAS and SNOT-22 scores) after 3 months of treatment (12 weeks). These findings were in agreement with those of previous studies<sup>(27-30)</sup>, but to our knowledge, this was the first time that these data were obtained from a double-blind, randomised, placebo-controlled trial in a specific and well-defined group. In the present study, tissue eosinophilia was evaluated according to the literature<sup>(26,31,32)</sup> by a pathologist (G.D.C.) who was blinded to the study procedures. Eosinophils are predominant inflammatory cells in CRSwNP and appear to play a key role in the etiopathogenesis of this disease. They are responsible for cytokine secretion related to the maintenance of the inflammatory course and tissue damage<sup>(33)</sup>. When related to the involvement of *Staphylococcus aureus* in nasal polyposis pathophysiology, mast cells and eosinophils participating in the inflammatory cascade are triggered by the presence of superantigens and perpetuate the present chronic inflammation<sup>(5)</sup>. This finding is quite relevant and in agreement with studies suggesting the effective use of macrolides in chronic rhinosinusitis disease with

low IgE levels<sup>(30,34)</sup>.

The treatment interval chosen in this study was based on the literature<sup>(35,36)</sup>. Furthermore, we noted the mid-range between the first appointment and surgery (usually 3 months at HC-UFMG). Thus, we tried not to burden patients with additional transportation to the hospital. Moreover, the study did not delay any previously recommended surgery, even where there was no improvement in symptoms after the proposed treatment application. However, in some studies, the improvement or benefits increased in accordance with the treatment duration<sup>(24,25,37,38)</sup>. Thus, in theory, we might have obtained even better results if the study had been prolonged for additional weeks. In chronic inflammatory lung diseases, azithromycin administration was maintained for longer periods without an increase in severe adverse effects at the dosage used by our team<sup>(21-23)</sup>.

As CRSwNP is a multifactorial disease, it is possible that a combination of treatments is required to obtain adequate symptom control. Based on this study's results, further investigations should evaluate a combination of clinical treatments, such as topical corticosteroid and azithromycin administration.

It is worth mentioning that the 1-year follow-up performed in this study is reported for the first time in the literature. We found that even after 12 months of completion of treatment, patients in the azithromycin group maintained a significantly lower SNOT-22 score than that noted in pretreatment. Interestingly, it is stated in the literature that the recurrence rate of polyposis, even after surgery, is high. Relapse rates of up to 50% have been reported by studies that followed patients for 2 to 5 years after surgery<sup>(10)</sup>.

One study showed that the administration of macrolides could result in prolongation of the QT interval and consequent torsades de pointes arrhythmia. Such risk is greater in the presence of cardiovascular risk factors (prolongation of the pre-existing QT interval, hypokalaemia, hypomagnesaemia, and bradycardia) and the concomitant use of antiarrhythmic drugs (e.g., quinidine, procainamide, and amiodarone), which can prolong the QT interval<sup>(39)</sup>. Additionally, recent studies have highlighted the safety of macrolides<sup>(40,41)</sup>, especially azithromycin<sup>(42)</sup>.

## Conclusion

Treatment with 500 mg azithromycin three times/week for a 12-week period led to significant clinical improvement based on subjective improvement as determined by a quality-of-life questionnaire (the SNOT-22) and polyp staging and a reduction in the number of eosinophils in polyp biopsies. In contrast, there were no such significant differences in the placebo group before and after the intervention. Additionally, the improvement in quality of life was maintained in the azithromycin group at the 1-year follow-up after treatment. Although the current literature indicates that treatment with azithromycin is recommended only in patients with CRS with low polyposis and IgE, the observed results in a specific group of patients were not expected. Additional studies should be conducted to perform neutrophil evaluations on histology and serum IgE dosing.

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## Authorship contribution

ISO: the main researcher responsible for patient enrolment and the only researcher to administer the questionnaires. AFG: responsible for patient enrolment and literature revision. GRAP performed the histomorphological analysis of biopsies. CJM performed the statistical analysis. GDC performed the histomorphological analysis of biopsies and was the main researcher. PFTBC was a main researcher. FBN was an assistant researcher. HMGB was an assistant researcher. RESG was a main researcher.

## Conflict of interest

The authors have no conflicts of interest to declare pertaining to this article.

## Full protocol available

<http://www.ensaioclinic.gov.br/rg/RBR-9pqppb/>

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Isamara Simas de Oliveira, MD, PhD  
 Post Graduate Program in Surgery  
 and Ophthalmology  
 Universidade Federal de Minas Gerais  
 Belo Horizonte  
 Minas Gerias  
 Brazil

Tel: +55 31 998846337

E-mail: simasmed@gmail.com