

# Long-Term Azithromycin Maintenance Treatment in Patients with Frequent Exacerbations of Chronic Obstructive Pulmonary Disease

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**Abstract:** Macrolides are effective in reducing the number of exacerbations in COPD patients with the frequent exacerbator phenotype. Our study did not show a persistent effect of azithromycin on exacerbation frequencies after more than one year of usage.

**Keywords:** Macrolide, long-term, exacerbations, COPD, COLUMBUS

## Introduction

Exacerbations of COPD have a major impact on the course of the disease. Frequent exacerbations can result in lower quality of life, faster in decline in lung function, higher mortality rate and has a major impact on the health care budget.<sup>1-4</sup>

Maintenance treatment with azithromycin during a period of one year resulted in a significant decrease in COPD exacerbations during that year.<sup>5-7</sup> However, there is little information about the long-term effect of azithromycin maintenance treatment for more than one year.

## Aims and Objectives

The aim of this study is to investigate if prolonged treatment for more than one year with azithromycin leads to a persistently decreased exacerbation frequency.

## Methods

The Medical Research Ethics Committee ErasmusMC (Rotterdam, The Netherlands) approved the study (MEC-2019-0536). All participants were given verbal and written information about the study purposes. Written informed consent was obtained from all study participants. The guidelines of the WMA declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) were followed.

We performed a single-center retrospective cohort study using the Columbus cohort (protocol at ClinicalTrials.gov NCT00985244) of the Amphia hospital, Breda. We analyzed two populations, within the group of patients treated with azithromycin: one group of patients continued azithromycin maintenance treatment after finishing the COLUMBUS study, the other group of patients stopped azithromycin after completion of the study year of treatment. The azithromycin treatment regimen used was 3 times a week one oral tablet of 500mg.

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All data on baseline characteristics, number of exacerbations, hospital admissions and lung function parameters during follow up were collected. Exacerbations were defined as events in which antibiotics or corticosteroids (or both) were prescribed or resulted in hospitalization (severe exacerbations). Exacerbations were observed for a period of 1 year.

Exacerbation frequency, time-to next exacerbation (TTE), number of hospital admissions and lung function parameter were reported as median [interquartile range] and between groups differences were analyzed using the Mann–Whitney *U*-test.

## Results

Results are shown in Table 1. Of the initial 47 patients who were treated with azithromycin during the Columbus trial, 41 completed the full 12-month follow up of the COLUMBUS trial. Of those 41 patients, 14 patients (34%) still used this medication in the consecutive year, the other 27 patients (66%) stopped with maintenance treatment after the COLUMBUS trial.

There was no significant difference in median exacerbation frequency in the continued azithromycin maintenance

group 1.5 [IQR 0–3.25] when compared to the non-maintenance group 1.0 [IQR 0–2.00],  $p=0.577$ . The median time to next exacerbation was 138 days [IQR 57–189] versus 168 days [IQR 91–222] days,  $p=0.11$ , and the median number of hospital admissions was 0.5 [IQR 0–3.25] versus 0 [IQR 0–1],  $p=0.307$ , for the continued azithromycin maintenance and non-maintenance group respectively.

At baseline neither the number of exacerbations ( $p=0.194$ ), nor the number of hospitalizations ( $p=0.115$ ) were significantly different between the continued azithromycin maintenance and non-maintenance groups.

The FEV1 percentage of predicted (FEV1%) value during the follow up was significantly lower in the azithromycin maintenance group,  $p=0.039$ . The median FEV1% was 30% [IQR 26–36%] in the azithromycin group, compared with 43% [IQR 34–54%] in the non-maintenance group. Compared to the baseline values of FEV1 in liters and FEV1%, we did not find a significant difference between the two groups,  $p=0.056$  and  $p=0.159$  respectively.

## Discussion

Long-term azithromycin usage for more than one year after finishing the COLUMBUS study did not result in

**Table 1** Data are n (%), Mean (SD), or Median (Range), Unless Otherwise Indicated

	Baseline	2nd Year of Follow-Up		P
	Azithromycin (N=41)	Azithromycin (N=14)	No-Maintenance (N=27)	
Men	22 (47%)	5 (36%)	15 (56%)	
Age	64.7 (10.2)			
COPD GOLD stages				
GOLD I	0 (0%)	0 (0%)	0 (0%)	NS
GOLD II	15 (36.6%)	2 (21.4%)	12 (44.4%)	NS
GOLD III	13 (31.7%)	4 (28.6%)	9 (33.3%)	NS
GOLD IV	13 (31.7%)	7 (50%)	6 (22.2%)	NS
Smoking	20 (43%)	7 (50%)	9 (33%)	
Pack years		40.3 (15.4)	39.2 (17.1)	NS
Total exacerbations median [IQR]	1.00 [IQR 0–3.00]	1.50 [IQR 0–3.25]	1.00 [IQR 0–2.00]	NS
Hospital admission/severe exacerbation median [IQR]	0 [IQR 0–1.00]	0 [IQR 0–3.00]	0 [IQR 0–1.00]	NS
Time-to-exacerbation (days) median [IQR]		138 [IQR 57–189]	168 [IQR 91–222]	NS
FEV1 (L) Median [IQR]	1.03 [IQR 0.72–1.26]^	0.81 [IQR 0.64–1.07]	0.96 [IQR 0.77–1.26]	NS
FEV1 (% predicted) Median [IQR]	42 [IQR 28–58]^	30 [IQR 26–36]	43 [IQR 34–54]	0.039

**Note:** ^Measurement at month 12 of the Columbus trial.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NS, not significant; IQR, interquartile range.

a significant decreased exacerbation frequency or a reduced number of hospital admissions.

The amount of publications regarding long-term continuous cycle azithromycin is limited. One study addressing this subject is performed by Pomares et al<sup>8</sup>. This group investigated the long term effects of azithromycin in 109 patients (with a COPD GOLD D classification and with four or more exacerbations in the previous year). Patients were treated with continued azithromycin during a short-term period of <24 months (N=70) or long-term period >24 months (N=39). In this study, a significant reduction in exacerbations was seen at 12 months (56.2%), at 24 months (70%) and at 36 months (41%), compared to baseline. The largest reduction was seen at 24 month, with a diminishing effect after 24 months. Unfortunately, those results of the azithromycin treated patients were not compared with a control group of patients, who did not receive azithromycin. Although the number of exacerbations by common micro-organisms (*H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and methicillin-susceptible *Staphylococcus aureus*) decreased by 12.5% at 12 months and 17.3% at 24 months, a 50% increase in macrolide resistance was seen by those common microorganisms. The incidence of exacerbations in the period of treatment with azithromycin caused by *Pseudomonas Aeruginosa* increased from 7.3% at 12 months to 13.1% at 24 months.

In a study performed by Samson et al the long term effect of azithromycin in cystic fibrosis patients was investigated.<sup>9</sup> In a cohort of 68 cystic fibrosis (pediatric) patients a significant reduction was seen in the number of pulmonary exacerbations and antibiotic courses needed in the first twelve months of treatment. This effect diminished after twelve months of treatment with azithromycin, with an increase to baseline numbers of pulmonary exacerbations and antibiotic courses needed. Macrolide resistance of staphylococcus aureus strains was seen in 100% of the cases after 6 months (29/68 patients), and the strains remained resistant during the 3 years of follow up.

With an increased prescription of macrolide antibiotics, a significant increase in macrolide resistance was observed.<sup>10</sup> Potential side effects of macrolides are gastrointestinal symptoms (mainly diarrhea), hearing impairment and even increased cardiovascular death.<sup>5,6,11</sup>

Azithromycin has proven to reduce the exacerbation frequency in COPD in the first twelve months of treatment; nonetheless, prolonged usage after 12 months might not be useful according to the results of this study. The retrospective aspect and limited number of patients in the

follow up period makes the results difficult to interpret. However, our results clarify that one has to evaluate in each individual patient whether a prolonged treatment for more than one year is justifiable. A possible explanation for the diminished effect of azithromycin after one year of treatment could be an altering in the patients microbiota and the development of macrolide resistance, causing again more bacterial exacerbations.<sup>9,12,13</sup> Future prospective randomized trials are needed to determine whether macrolide treatment for more than one year in COPD patients can still be beneficial.

## Disclosure

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