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Original Article

Azithromycin on serum FeNO, IgE, and eosinophil levels in bronchiectasis patients

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Abstract

Background: Azithromycin, a macrolide antibiotic with notable anti-inflammatory properties, is widely used in the treatment of bronchiectasis. This study aimed to assess changes in serum fractional exhaled nitric oxide (FeNO), immunoglobulin E (IgE), and eosinophils levels before and after azithromycin treatment in bronchiectasis patients.

Methods: A retrospective cohort study was conducted at Rasul Akram Hospital involving bronchiectasis patients. Participants were evaluated in two phases: before receiving azithromycin (500 mg on every other day) and three months following oral azithromycin treatment. Demographic data, medical history, and baseline FeNO, IgE, and eosinophil levels were collected during the initial visit. These biomarkers were measured again at the follow-up visit.

Results: The study included 50 participants, with a mean (±SD) age of 40.78 (±5.45) years; 48% were females, and 52% were males. FeNO levels showed a significant decrease from 47.64±16.20 ppb at baseline to 18.6 ±5.99 ppb post-treatment ($p<0.001$). IgE levels also declined significantly from 747.90±166.87 IU/mL initially to 280.40±115.93 IU/mL ($p<0.001$). Additionally, eosinophil counts decreased from an initial mean of 687.00±199.18 cells/µL to 236.30±203.17 cells/µL at post-treatment ($p<0.001$). Patients with mild and moderate bronchiectasis exhibited significant reductions in inflammatory markers ($p<0.001$), those with more severe bronchiectasis did not show a comparable level of improvement. Gender and smoking status had no significant impact on treatment outcomes.

Conclusion: Azithromycin administration significantly improved IgE, FeNO, and eosinophil serum levels, underscoring its therapeutic potential in modifying bronchiectasis-related inflammation.

Keywords: Bronchiectasis, Azithromycin, IgE, FeNO, Eosinophil.

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Bronchiectasis is a chronic respiratory condition characterized by irreversible dilation of the bronchi, leading to significant morbidity and frequent respiratory infections. Bronchiectasis is increasingly recognized across various age groups and early diagnosis and management are crucial (1). The pathophysiology of bronchiectasis involves a complex interplay of chronic inflammation, airway infection, and mucociliary dysfunction, contributing to a cycle of progressive lung damage (2). A post-infectious etiology accounts for 30.5% of cases globally (3), and 30–40% of cases have an unknown etiology (2). The global prevalence of bronchiectasis is reportedly increasing, making it the third most common chronic airway disease after chronic obstructive pulmonary disease (COPD) and asthma (4). Recent studies have estimated the prevalence of non-cystic fibrosis bronchiectasis to be approximately 39.9 cases per 100,000 individuals (5), with higher rates in low- and middle-income countries, where historical factors such as tuberculosis contribute to its prevalence (6).

The primary cause of death in bronchiectasis is often respiratory failure, with survival rates reported at 91% at 4 years and 68.3% at 12 years. Chronic infection with *Pseudomonas aeruginosa* is also linked to higher mortality rates (7). The chronic inflammatory process in patients with bronchiectasis often results in elevated levels of fractional exhaled nitric oxide (FeNO), immunoglobulin E (IgE), and eosinophils (8). This inflammation is driven by a heightened neutrophilic response due to abnormal activation of proinflammatory cytokines such as interleukin-1b, interleukin-8, TNF-α, and leukotrienes (9). Elevated levels of hydrogen peroxide, superoxide anion, 8-isoprostane, and reactive nitrogen species in exhaled air are also observed in patients with cystic fibrosis, bronchiectasis, and COPD (10). The connection between changes in eosinophil count, FeNO, and IgE levels and lung function in bronchiectasis is significant (11). Elevated eosinophil counts and FeNO are indicative of type 2 inflammation, which correlates with exacerbation rates, clinical outcomes, and quality of life in patients with bronchiectasis (12). Eosinophilic bronchiectasis is associated with worse lung function and higher exacerbation rates. Patients with eosinophilic bronchiectasis had a 28% increased risk of reduced lung function compared to non-eosinophilic patients (13). Inhaled corticosteroids reduced exacerbation rates in eosinophilic patients, highlighting the importance of eosinophil levels in treatment response (14). High FeNO levels correlate with better lung function and fewer affected lobes, suggesting that FeNO can serve as a positive prognostic marker (15). Conversely, decreased FeNO is an independent predictor of disease severity, indicating its dual role in assessing bronchiectasis outcomes (15). Elevated IgE levels are often associated with allergic responses and may contribute to the severity of bronchiectasis, although specific studies linking IgE diretly to clinical outcomes in bronchiectasis are limited.

Early diagnosis and effective infection management can stabilize the disease and improve outcomes. Current treatments for bronchiectasis include antibiotics (oral, inhaled, or intravenous), mucolytics, and physical therapy. Adherence to complex treatment regimens, including inhaled antibiotics and chest clearance techniques, is critical but often challenging for patients; poor adherence is associated with worse outcomes and higher exacerbation rates (16). Intensified infections in bronchiectasis are associated with significant complications, with approximately 38% of patients experiencing three or more exacerbations annually (17). In Europe and the Americas, bronchiectasis exacerbation rates three or more per year (18). While various antibiotics are available for controlling bacterial infections during exacerbations, evidence suggests that certain treatments have additional benefits. For example, macrolides are shown to reduce the frequency of exacerbations, slow lung function decline, and improve quality of life and survival rates (19). Long-term macrolide therapy is effective in reducing exacerbation frequency in both COPD and bronchiectasis patients (19). Macrolides are unique among bronchiectasis treatments for their dual antibacterial and immunomodulatory effects, which have been proven in randomized, double-blind, placebo-controlled trials to reduce exacerbation rates in Non–cystic fibrosis bronchiectasis patients (20, 21).

Azithromycin, a macrolide with anti-inflammatory properties, is widely used in bronchiectasis management. Long-term prophylactic use of azithromycin has been shown to reduce exacerbation frequency, decrease sputum production, and improve lung function in non-cystic fibrosis bronchiectasis (22). However, evidence regarding azithromycin's efficacy in non-cystic fibrosis bronchiectasis is controversial (23). The effects of azithromycin on FeNO levels, IgE, and eosinophil counts in bronchiectasis patients remain unclear. This study aimed to determine changes in serum IgE, FeNO, and eosinophil levels before and after azithromycin administration in bronchiectasis patients.

Methods

The study was conducted using a retrospective cohort method at a university-affiliated hospital (Rasool-e-Akram) in Tehran, Iran, between April 2023 and April 2024. The local Ethics Committee of Iran University of Medical Sciences has approved this study (Ethical Registration No.: IR.IUMS.FMD.REC.1402.313). Eligible patients with bronchiectasis were selected according to the available sampling method. Informed consent was obtained from the patients before recording data.

The inclusion criteria were; age over 18 years, known case of bronchiectasis, no intake of azithromycin in the last 30 days, no sensitivity or allergy to azithromycin or similar drugs, no pregnancy or lactation, no history of COPD, asthma, or other respiratory diseases, no history of cardiac, hepatic, renal or other diseases that could affect the results of the study, no intake of medications that could affect the results, such as corticosteroids or immunosuppressants, interest and ability to participate in the course of the study and in the regular follow-up examinations. Patients with incomplete information in the study forms and who had not signed a consent form were excluded. According to the study by Xu et al. (24), the changes in FeNO without

treatment were 10%. It is expected that the changes with azithromycin treatment will be about 35% (Δ=0.25). Considering α=0.05 and β=0.2 and using the following formula, the sample size of 43 subjects was determined and 50 subjects were selected with an attrition rate of 20%.

$$N = \left\{ z_{1-\frac{\alpha}{2}} \times \sqrt{\bar{p} \times \bar{q} \times \left(1 + \frac{1}{k}\right)} + z_{1-\beta} \times \sqrt{p_1 \times q_1 + \left(\frac{p_2 \times q_2}{k}\right)} \right\}^2 / \Delta^2 = 43$$

Azithromycin 500 mg was administered every other day for a duration of three months. Patients were monitored through weekly telephone follow-ups, and scheduled in-person visits on specific dates were arranged to ensure adherence to the prescribed medication regimen. The study participants were examined in two phases, once before treatment with azithromycin (pre-treatment) and once after 3 months of oral azithromycin treatment (post-treatment). During the first visit, laboratory values (serum FeNO, IgE, and eosinophil levels) and patient characteristics (age, gender, medical history, and smoking) were recorded on forms at baseline and these variables were measured again at the patients' follow-up visit 3 months later.

The severity of the disease was determined based on the bronchiectasis severity index (BSI) (25). The BSI is a validated tool designed to assess disease severity and predict outcomes in patients with bronchiectasis, such as mortality, hospitalization, and exacerbation risks. The BSI, developed by Chalmers and colleagues, incorporates several clinical variables and its score is calculated by assigning points based on specific criteria. Age is scored with 0 points for patients under 50 years, 2 points for those aged 50-69, and 3 points for those 70 or older. Body mass index (BMI) is factored in, assigning 0 points for BMI ≥18.5 and 2 points for BMI <18.5. Lung function, measured as predicted FEV1%, is scored as 0 points for ≥80%, 1 point for 50–79%, 2 points for 30–49%, and 3 points for <30%. Prior hospitalizations in the last two years contribute 0 points for none, 1 point for one hospitalization, and 2 points for two or more. Exacerbations requiring antibiotics over the last year add 0 points if none, 1 point if there was one, and 2 points for two or more. Colonization with *Pseudomonas aeruginosa* adds 3 points, while colonization with other pathogens adds 1 point. Radiological severity, based on CT findings, is scored with 0 points if fewer than three lobes are affected and 1 point if three or more lobes are affected. Finally, dyspnea is scored using the MRC scale, with 0 points for grades 1–3, 1 point for grade 4, and 2 points for grade 5. These scores are summed to categorize patients into low (0–4 points), moderate (5–8 points), or high-risk (9 or more points) groups, guiding clinical management and prognosis. This scoring aids clinicians in treatment planning and enables more personalized management for those with bronchiectasis, supporting both prognostication and targeted interventions. Each of the factors contributes points, allowing patients to be stratified into mild (0–4 points), moderate (5–8 points), or severe (9 or more points) categories.

Descriptive statistics were used to analyze the characteristics of the study population. Changes in serum FeNO, IgE, and eosinophil levels pre- and post-treatment with Azithromycin administration were compared using paired t-tests or Wilcoxon signed-rank tests, depending on the data distribution. Multivariate regression analysis was performed to investigate the relationship between changes in FeNO, IgE, and eosinophil serum levels and changes in clinical symptoms and disease severity. P values less than 0.05 were considered statistically significant. SPSS version 22 (SPSS Inc., Chicago, IL., USA) was used for analysis.

Results

The patients participating in the study had a mean (SD) of 40.78 (5.45) years. 24 (48%) of the patients were females and 26 (52%) were males. 14 (28%) of the patients smoked in the past or present and 36 (72%) did not smoke. The severity of the disease was mild type in 18(36%) patients, moderate type in 29 (58%) patients, and severe type in 3 (6%) patients. Table 1 shows the mean (SD) serum levels of FeNO, IgE, and eosinophils before and after treatment with azithromycin.

Table 1. Comparison of serum FeNO, IgE, and Eosinophil levels at pre- and post-treatment with Azithromycin (n=50).

Variables (Mean±SD)	Pre-treatment	Post-treatment	P-value
FeNO (ppb)	47.64±16.27	18.68±5.99	0.001*
IgE (IU/mL)	747.90±166.87	280.40±115.93	0.001*
Eosinophil (cells/μL)	687.00±199.18	236.30±203.17	0.001*
Eosinophil (%)	6.24±1.28	1.90±1.40	0.001*

Note: Paired t-test was used. FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; n: number of participants; SD: standard deviation; p: probability-value. *Significant.

The serum levels of IgE, FeNO, and eosinophils before and after treatment with azithromycin were significant in patients according to gender (table 2). The serum levels of IgE, FeNO, and serum eosinophils before and after treatment with azithromycin were significant in patients

who were smokers or non-smokers (table 3). The serum levels of IgE, FeNO, and eosinophils at pre- and post-treatment with azithromycin were significant in patients with mild and moderate grades of disease, but in patients with severe disease, the difference at pre- and post-treatment with azithromycin was not significant (table 4).

Table 2. Comparison of serum FeNO, IgE, and Eosinophil levels at pre- and post-treatment with Azithromycin by gender (n=50).

Variables (Mean±SD)	Female		Male	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
FeNO (ppb)	41.58±10.73	17.08±5.28	53.23±18.58	20.15±6.33
P-value	0.001*		0.01*	
IgE (IU/mL)	695.42±169.78	251.67±109.65	796.35±151.57	306.92±117.29
P-value	0.001*		0.001*	
Eosinophil (cells/µL)	610.41±65.90	245.00±275.25	757.69±250.87	228.26±105.19
P-value	0.001*		0.001*	
Eosinophil (%)	5.70±0.80	2.01±1.81	6.73±1.45	1.80±0.89
P-value	0.001*		0.001*	

Note: Wilcoxon signed ranks test was used., FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; n: number of participants; SD: standard deviation; p: probability-value. *Significant.

Table 3. Comparison of serum FeNO, IgE, and Eosinophil levels at pre- and post-treatment with Azithromycin based on smoking (n=50).

Variables (Mean±SD)	Non-smoking		Smoking	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
FeNO (ppb)	45.25±12.78	17.86±5.15	53.79±22.39	20.17±7.57
P-value	0.001*		0.001*	
IgE (IU/mL)	733.89±169.62	267.22±113.17	783.93±159.85	314.29±120.23
P-value	0.001*		0.001*	
Eosinophil (cells/µL)	665.27±199.57	234.58±234.20	742.85±194.00	240.71±88.79
P-value	0.001*		0.001*	
Eosinophil (%)	6.08±1.18	1.92±1.58	6.64±1.49	1.84±0.78
P-value	0.001*		0.001*	

Note: Wilcoxon signed ranks test was used. FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; n: number of participants; SD: standard deviation; p: probability-value. *Significant.

Table 4. Comparison of serum FeNO, IgE, and Eosinophil levels at pre- and post-treatment with Azithromycin based on disease severity (n=50).

Variables (Mean±SD)	Mild		Moderate		Severe	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
FeNO (ppb)	52.50±20.38	20.61±6.95	45.21±13.57	17.69±5.22	42.00±5.29	16.67±5.77
P-value	0.001*		0.001*		0.08	
IgE (IU/mL)	819.17±228.35	329.44±145.94	717.24±103.67	254.83±87.81	616.67±57.73	233.33±76.37
P-value	0.001*		0.001*		0.08	
Eosinophil (cells/µL)	788.88±277.88	217.22±92.78	641.37±102.70	256.55±253.36	516.66±28.86	155.00±142.56
P-value	0.001*		0.001*		0.08	
Eosinophil (%)	6.72±1.48	1.79±0.93	6.06±1.09	2.02±1.66	5.00±0.00	1.36±1.09
P-value	0.001*		0.001*		0.08	

Note: Wilcoxon signed ranks test was used. FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; n: number of participants; SD: standard deviation; p: probability-value. *Significant.

Discussion

This study evaluated the effects of azithromycin on inflammatory markers serum IgE, FeNO, and eosinophil levels in patients with bronchiectasis. Our findings indicate that azithromycin administration significantly improved these markers, underscoring its therapeutic potential in modifying bronchiectasis-related inflammation. FeNO, a marker of airway inflammation, has shown varying levels across bronchiectasis patient profiles. Elevated FeNO levels are generally associated with type 2 inflammation, which may correlate with better lung function and fewer affected lobes (26). In this study, FeNO levels significantly decreased following azithromycin treatment, suggesting a reduction in airway inflammation. This aligns with prior research demonstrating lower FeNO in bronchiectasis patients than in asthma, where levels are typically higher (26). The decrease in FeNO from 47.64±16.20 ppb to 18.68±5.99 ppb supports findings by Cho et al., who reported that FeNO levels in stable bronchiectasis were significantly lower than in asthma and COPD, with a mean FeNO of 18.8±1.5 ppb (26). However, studies have noted the limited utility of FeNO in assessing stable bronchiectasis severity (27), emphasizing the need for a more targeted evaluation of its role in distinguishing patient subtypes.

FeNO's diagnostic utility has been explored in differentiating bronchiectasis patients with asthma from those without, with studies establishing a threshold of >22.5 ppb (28). FeNO levels tend to be lower in bronchiectasis patients with nontuberculous mycobacterial infections (26). Our findings, showing reduced FeNO after azithromycin, highlight its potential as a biomarker for airway inflammation in bronchiectasis management. Elevated IgE levels have been linked to increased disease severity in bronchiectasis. Studies indicate that higher IgE levels are associated with longer disease duration, a history of allergic disease, and worse lung function. Similarly, the reduction in serum IgE levels (from 747.90±166.87 IU/mL to 280.40±115.93 IU/mL) aligns with Hassan et al.'s study, which found that bronchiectasis patients with high IgE levels had significantly worse FEV_1 (49.38±12.65; P = 0.041) and FEV_1/FVC (60.89±13.52, P = 0.015) values, more extensive HRCT abnormalities, and greater bronchial reversibility (29). Elevated IgE is more common in idiopathic bronchiectasis, presenting an immunological profile distinct from conditions like allergic bronchopulmonary aspergillosis (30). Our findings add to the understanding of the complex immune profile in bronchiectasis, suggesting that IgE levels may serve as a marker for disease severity and allergic sensitization. While some studies did not find significant differences in IgG subclasses (31), elevated IgE highlights the role of immune dysregulation in bronchiectasis, warranting further investigation. Regarding eosinophilia, our study found a substantial reduction in eosinophil counts (from 687.00 ± 199.18 cells/μL to 236.30±203.17 cells/μL), corroborating previous research that links eosinophilia to bronchiectasis severity and exacerbation risk. While Cho et al. (26) noted a positive correlation between FeNO (18.8±1.5) and eosinophil counts (152.9±134.7) in airway diseases, in our patients both biomarkers decrease significantly with azithromycin therapy, suggesting a shared inflammatory pathway influenced by macrolide treatment. Eosinophilia (≥300 cells/μL) in bronchiectasis patients has emerged as a potential marker of disease severity, with higher eosinophil counts correlating with more severe disease, higher exacerbation rates, and lower lung function (32, 33).

Our study findings align with recent evidence that associates high eosinophil levels with increased bronchiectasis severity scores, such as the BSI and E-FACED scores (The E-FACED score is a validated tool for assessing bronchiectasis severity and prognosis based on six parameters: exacerbations, FEV_1 (% predicted), age, Pseudomonas aeruginosa colonization, radiological extent, and dyspnea (mMRC) scale. The total score (0–9) categorizes disease severity as mild (0–3), moderate (4–6), or severe (7–9). Higher scores indicate worse outcomes, making E-FACED valuable for risk stratification and guiding clinical management.). Interestingly, a U-shaped relationship has been observed, where both high and low eosinophil counts correlate with severe disease (34), indicating the need for personalized approaches based on eosinophil levels. Azithromycin's efficacy in bronchiectasis treatment has been well-documented, particularly in reducing exacerbation rates. In our study, azithromycin treatment was associated with improved inflammatory markers, such as IgE, FeNO, and eosinophil levels. Previous trials, like the BAT trial, have shown a median reduction in exacerbations with azithromycin (35), supporting its benefit in managing bronchiectasis. In the present study, gender and smoking history did not significantly impact the reduction in IgE, FeNO, and eosinophil levels following azithromycin treatment. Moreover, our findings align with some previous studies (36, 37) which indicated that smoking history does not significantly influence FeNO levels. This suggests that azithromycin's effects on inflammatory markers may be broadly effective across different demographic profiles, irrespective of smoking status. Our findings showed that patients with mild and moderate bronchiectasis exhibited significant reductions in

inflammatory markers, those with more severe bronchiectasis did not show a comparable level of improvement. This lack of response in severe cases could reflect a threshold in disease progression beyond which inflammation becomes less modifiable by macrolide therapy alone. These results highlight the potential for stratifying patients by disease severity when considering azithromycin therapy, as individuals with less advanced disease might derive greater benefit. However, based on our findings, only three patients (6%) had severe bronchiectasis; therefore, the data are insufficient to conclude that azithromycin is ineffective in reducing inflammatory markers in this patient subgroup. Given the limited sample size, however, further studies are needed to confirm these findings and explore additional therapeutic approaches for patients with severe bronchiectasis, where inflammatory processes may be more entrenched.

Assessing changes from baseline to post-treatment provides a practical approach to evaluating treatment effects in bronchiectasis. However, this study had some limitations, including a small sample size and relatively short treatment duration of 12 weeks. Moreover, a key limitation of this study is the absence of a control group, which restricts the ability to definitively attribute changes in FeNO to azithromycin treatment. This limitation arises from the retrospective study design and challenges in recruiting a comparable control group, highlighting the need for future controlled studies. Also, longer studies with larger cohorts and more frequent inflammatory marker measurements are needed to elucidate the full impact of azithromycin on inflammatory markers and long-term outcomes. Although our study did not specifically assess clinical parameters such as symptom severity or lung function, the observed reductions in inflammatory markers suggest a potential therapeutic benefit, emphasizing the need for further research to establish these associations. Additionally, further investigation into eosinophilic phenotypes in bronchiectasis could provide insights into more personalized treatment strategies, particularly concerning the use of corticosteroids in eosinophilic patients without asthma. Azithromycin administration significantly improved IgE, FeNO, and eosinophil serum levels, underscoring its therapeutic potential in modifying bronchiectasis-related inflammation. Future prospective studies with control groups and comprehensive clinical assessments are essential to confirm the potential benefits of azithromycin in bronchiectasis and to establish a clearer link between biomarker changes and patient outcomes.

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Ethics approval: This study was designed based on the ethical principles of the Declaration of Helsinki (2008) for medical studies involving humans. The local Ethics Committee affiliated with the Iran University of Medical Sciences has approved this study (Ethical Registration No.: IR.IUMS.FMD.REC.1402.313). Informed consent was obtained from the patients before recording data.

Conflict of interests: The authors declare no conflict of interest.

Authors' contribution: Niloofar Keikhaei, Conceptualization, Methodology, Data collection, Investigation, Writing – original draft; Seyedeh Hatameh Asadinejad Tahergourabi, Investigation, Data collection; Seyed Ali Javad-Mousavi, Formal analysis, Data curation, Writing – review and editing; Vahan Moradians, Supervision, Methodology, Writing – review and editing. All authors discussed and contributed to the final version of the manuscript.

Availability of supporting data: The data that support the findings of this study are available from the corresponding author (moradiansva@yahoo.com, moradians.v@iums.ac.ir) upon reasonable request.

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