Am J Transl Res 2021;13(6):7370-7375
www.ajtr.org /ISSN:1943-8141/AJTR0128886

Original Article

Effects of azithromycin on treating chronic obstructive pulmonary disease with acute exacerbation of chronic bronchitis in the stable phase

Yangfei Lu, Xiaobo Wang, Jun Zhao

Department of Respiratory Medicine, The First People's Hospital of Fuyang Hangzhou, Hangzhou 311400, Zhejiang 311400, China

Received December 23, 2020; Accepted March 19, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Objective: To explore the effects of azithromycinon in treatment of chronic obstructive pulmonary disease (COPD) in patients with acute exacerbation (AE) of chronic bronchitis (CB) in the stable phase. Methods: Totally, 60 COPD patients with AE of CB were divided into control group (CG, 30 cases) and experimental group (EG, 30 cases) using the random number residue method. The CG was administered 250 mg salmeterol-fluticasone powder inhalation twice a day combined with 18 μg tiotropium bromide inhalation once a day. The EG was treated with 250 mg azithromycin tablets once a day in addition to the treatment of the CG. We compared the clinical effect, pulmonary function, and fractional exhaled nitric oxide index between two groups after treated for three-months. Results: Compared with the CG, the EG showed a better clinical effect with a total effective rate at 86.67% after treatment (P<0.05). The EG exhibited better FEV1 and FEV1% than the CG (P<0.05). We also observed the difference between clinically FeNO-invalid patients before and after treatment was significant (P<0.05). After treatment, this difference among groups was statistically significant (P<0.05). Conclusions: Azithromycin combined with salmeterol-fluticasone powder inhalation and tiotropium bromide inhalation have good effects for treating COPD patients with AE of CB in the stable stage and can improve the pulmonary function. When COPD with AE of CB was exacerbated, the FeNO index increased significantly, indicating a potential increase in the mucosal inflammatory cells and eosinophils of the airway.

Keywords: Azithromycin, chronic bronchitis, chronic obstructive pulmonary disease, fractional exhaled nitric oxide

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory diseases in clinical practice characterized by a high recurrence rate, morbidity, and mortality [1-3]. Its long disease course warrants long-term therapy, which brings about a great financial burden on patients, their families, and society [4]. The Spanish guidelines for management of COPD (GesEPOC) [5] in 2017 recommended phenotypic typing only for patients with high-risk COPD, which can be classified into four subtypes: (1) non-acute exacerbation phenotype; (2) ACO; (3) acute exacerbation of emphysema; (4) acute exacerbation of chronic bronchitis (CB). CB [6] presents with symptoms such as cough and sputum, which lasts for more than 2 years; the symptoms in each year typically last more than 3 months. High-resolution computed tomography (HRCT) is recommended to determine bronchiectasis in patients. A sputum culture should be performed during the stable phase especially when it appears yellow or gray. Repeated positive results of sputum culture indicate CB in patients. In terms of fractional exhaled nitric oxide (FeNO), the eosinophilic inflammation of the airway is the main reason for the increase of FeNO in patients with asthma [7] who show a positive correlation. Since COPD was accompanied by eosinophilia, different changes are expected in FeNO COPD. It has been reported that COPD patients displayed many clinical symptoms even if they were in stable stage. For example, there were still sputum symptoms in the morning and night. When the expectoration of sputum becomes difficult, the risk of suffocation

Table 1. Gender and age differences between two groups

Group	Number of cases	Male (%)	Age (mean ± SD)
control group	30	25 (83.33%)	65.7 ± 12.5
Experience group	30	21 (70%)	64.9 ± 12.1
T (x^2) value	-	1.4907	0.2581
P value	-	0.2221	0.8021

increases and can seriously affect the quality of life and pose significant danger to the patient [1, 2]. Treatment using salmeterol-fluticasone combined with tiotropium bromide presented poor clinical efficacy and the occurrence of acute exacerbation and hospitalization increased greatly [8, 9]. Thus, in this study, azithromycin combined with salmeterol-fluticasone and tiotropium bromide was used to treat COPD patients with acute exacerbation of CB in the stable stage.

Information and methods

General information

60 patients with COPD who were admitted in the hospital between January 2018 and May 2019 were enrolled in the study. The inclusion criteria were as follows: patients 40-85 years of age who had suffered at least two acute exacerbations or one hospitalization in the most recent year; patients whose clinical manifestations were consistent with the CB phenotype defined in the GesEPOC guidelines of 2017; and patients without an acute exacerbation in the recent 4 weeks. The exclusion criteria were as follows: The inclusion criteria were as follows: Combined with other lung diseases that affect the patient's airflow, combined with other diseases that affect sleep quality such as narcolepsy, severe myocardial infarction, arrhythmia, tumors (need to take analgesics), severe liver and kidney dysfunction and other serious diseases; Patients with severe mental illness and cognitive communication impairment, unable to complete the questionnaire; taking drugs that affect sleep, such as sedative hypnotics, etc. All patients voluntarily participated in the research. Signed informed consent was obtained from each patient and approved by the ethics committee of The First People's Hospital of Fuyang Hangzhou.

Using the random number residue method, patients were divided into control group (CG) and experimental group (EG) with 30 patients in each group. There were 25 male and 5 female patients in the control group, with the mean age being 65.7 ± 12.5 years. In the EG, there were 21 male and 9 female patients, with the mean age being 64.0 ± 12.1 years. The general conditions of the two groups were compared using statistical methods and the difference was not found to be significant (P>0.05) with comparable comparison (**Table 1**).

Treatment

The control group was treated with 250 mg salmeterol-fluticasone powder inhalation twice a day and 18 μg tiotropium bromide inhalation once a day; the treatment period was 3 months.

The EG was treated with 250 mg azithromycin tablets once a day on the basis of the treatment of the CG; the treatment period was 3 months.

Observation indicators

Clinical effect evaluation standard: (1) Clinical effect. 1. Obvious clinical effects: after treatment, the clinical manifestations and signs basically disappeared, which were examined using doctor's auscultation; the patient's pulmonary rales disappeared and chest CT showed obvious absorption. 2. General clinical effects: after treatment, the patient's clinical performance and signs improved and the pulmonary rales decreased, but did not disappear; chest CT showed a little absorption. 3. Ineffective clinical effect: after treatment, the clinical manifestations and signs of patients did not improve; chest CT showed no absorption or aggravation. (2) Pulmonary function and other indicators, including FEV1, FVC, FEV1%, FEV1/FVC, and FeNO.

Statistical analysis and discussion on statistical processing

The data were analyzed using SPSS22.0 statistical software and are expressed as x ± s. The evaluation on the curative effect before and after treatment was performed using paired chi-square test and P<0.05 was considered as statistically significant.

Table 2. Comparison of COPD parameters before treatment

Group	Number of cases	FEV1	FEV1%	FEV1/FVC	FeNO	FVC
Control group	30	1.3 ± 0.6	51.1 ± 18.6	58.3 ± 10.5	24.3 ± 10.7	2.3 ± 0.80
Experiment group	30	1.5 ± 0.6	59.9 ± 22.5	57.8 ± 10.1	26.8 ± 11.9	2.5 ± 0.82
T value	-	1.05	1.647	0.211	0.857	1.089
P value	-	0.297	0.105	0.834	0.395	0.281

Table 3. Comparison of the clinical effects of two groups after treatment

Group	n	Significant effect	General effect	Ineffective	Total efficiency rate**
control group	30	8 (26.67%)	10 (33.33%)	12 (40%)	60.00%
Experiment group	30	17 (56.67%)	9 (30.00%)	4 (13.33%)	86.67%
X^2			7.293		
P			0.026*		

*P<0.05 indicated statistical difference, **total effective rate = significant effect + general effect.

Table 4. Comparison of pulmonary function and FeNO of the two groups after treatment

Group	n	FEV1/FVC	FEV1	FEV1%	FeNO	FVC
Control group	30	59.3 ± 10.7	1.30 ± 0.5	54.1 ± 17.6	38.2 ± 43.0	2.3 ± 1.0
Experiment group	30	61.2 ± 14.9	1.6 ± 0.6	64.8 ± 20.7	25.5 ± 16.6	2.5 ± 0.7
t	-	0.574	2.013	2.164	1.569	0.882
P	-	0.568	0.049*	0.035*	0.222	0.381

Note: *P<0.05 indicated statistical significance.

Results

Baseline information show no significant difference

Tables 1 and **2** show that there was no statistical difference in the gender, age, FEV1, FEV1%, FEV1/FVC, FVC, and FeNO indices between the control and experiment groups (P>0.05), indicating that the two groups were comparable.

The clinical effects in the experiment group were better than those of the CG

Table 3 shows that the clinical effects in the experiment group were better than those of the CG with a total efficacy rate of 86.67%, which was higher than that of the CG (60%). This difference was statistically significant (P<0.05). After treatment, the comparison among FEV1/FVC, FVC, and FeNO presented no statistical difference (P>0.05) (**Table 4**).

The paired pulmonary function parameters including FEV1, FEV1%, FEV1/FVC, and FVC in the two groups before and after treatment

Table 5 shows that the paired pulmonary function parameters including FEV1, FEV1%, FEV1/FVC, and FVC revealed no statistical difference (P>0.05) before and after treatment in the CG. Additionally, there was no statistical significant difference between the two groups. **Table 5** indicates that the comparison of pulmonary function indicators such as FEV1, FEV1%, and FEV1/FVC in the experiment group before and after treatment were statistically significant (P<0.05), while the comparison of FVC showed no statistical significance (P>0.05).

Comparison of FeNO levels in clinical inefficiency patients before and after treatment presented a statistical significance

Data in **Table 6** suggests that the comparison of FeNO levels in clinical inefficiency patients before and after treatment presented a statistical significance (P<0.05), while the comparison between the other two groups did show statistical significance (P>0.05). Before treatment, the comparison of FeNO levels in three clinical effect group exhibited no statistical significance (P>0.05). However, after treatment, a significant difference was observed when the clinical inefficiency was compared in patients between the remaining two groups (P<0.05).

Table 5. Comparison of pulmonary function indices, before and after treatment in the control group and experiment group

		n	FEV1/FVC	FEV1	FEV1%	FVC
Control group	*d* + *Sd*	30	0.16 ± 10.85	0.01 ± 0.26	3.86 ± 10.76	0.79 ± 0.62
	t	-	0.080	0.298	1.964	0.692
	P	-	0.937	0.768	0.059	0.494
Experiment group	*d* + *Sd*	30	3.97 ± 8.72	0.12 ± 0.24	4.76 ± 10.08	0.05 ± 0.23
	t	-	2.495	2.834	2.585	1.256
	P	-	0.002*	0.008*	0.015*	0.219

*Note: *P*<0.05 indicated statistical significance.

Table 6. Comparison of FeNO indices of the two groups before and after treatment

Group	Significant effect	General effect	Ineffective	F	P
n	25	19	16	-	-
FeNO before treatment	28.8 ± 10.9	20.1 ± 10.4	27.1 ± 11.0	0.424	0.656
FeNO after treatment	20 ± 8.8	23.3 ± 15.2	58.3 ± 96.9	9.085	0.0004*
t	3.08	1.43	2.60	-	-
P	0.051	0.17	0.02*	-	-

*Note: *P*<0.05 indicated statistical significance.

Discussion

COPD is a complex and heterogeneous disease. Its complexity lies in that COPD contains many intrapulmonary and extrapulmonary mechanisms and their interactions are different and vary between time and regions [10, 11]. The heterogeneity referred to the fact that not all mechanisms would occur in patients at the same time [12]. FEV1 cannot objectively reflect the complexity and heterogeneity of COPD nor reflect its pathophysiological mechanisms [13]. For example, CB, emphysema, or their co-existence can cause a decrease in FEV1 [14]. Therefore, some scholars propose categorizing phenotypes and its subtypes. Phenotype [5] is a description of the disease attributes (single or multiple) among COPD patients, which is closely related to clinical prognosis (symptoms, acute exacerbation, response to treatment, and disease progression rate, or death). This definition has two interpretations: (1) Unlike pulmonary function indicators (such as FEV1) that are ubiquitous among individuals. (2) It is closely related to the clinical prognosis in the future. The clinical phenotype of COPD cannot reflect the intrinsic pathophysiological mechanism of the disease, nor can it indicate the response to potential therapeutic regimens. As a result, the concept of a subtype corresponding to phenotype has been considered. A subtype [15] is defined as a disease pattern based on different functions or pathophysiological mechanisms. The relationship between subtypes and phenotypes is that subtypes can produce one or more clinical phenotypes, while the clinical phenotype is the comprehensive result of multiple subtypes. The occurrence of clinical symptoms had its own mechanism. Understanding the pathophysiology of the mechanism can help in further enhancing and increasing the precision of treatment in COPD patients [16, 17]. Additionally, giving due consideration to subtypes and phenotypes can help maximize the ratio of benefit to risk.

It can be concluded from this study that azithromycin was effective in the treatment of COPD in patients with acute exacerbation of CB. As a macrolide antibiotic, azithromycin inhibits bacterial protein synthesis and displays potent antibacterial effect in gram-positive and -negative bacteria [18]. Studies have shown that [19, 20] 14-16-membered macrolides can exert immunomodulatory and anti-inflammatory roles. Azithromycin is structurally a 15-membered macrolide ring exhibiting these properties. In addition, studies have also shown that azithromycin can be used in conjunction with glucocorticoids to achieve anti-inflammatory effects [21, 22]. The specific

mechanisms by which these effects are achieved are: 1. By affecting inflammatory factors, controlling neutrophil activity, and relieving airway inflammation in patients. 2. By controlling neutrophil adhesion and oxidative burst and accelerating the apoptosis of neutrophils. Inflammation has always been the primary pathogenesis for the occurrence and development of COPD. Chronic inflammation in the pulmonary parenchyma and vessels is regarded as a characteristic change brought about by COPD. The number of neutrophils and T lymphocytes in COPD patients increases significantly and inflammatory mediators such as IL-8, LTB4, and TNF-α are generated. Under the chemotaxis of these mediators, more inflammatory cells are activated and inflammatory cell networks appear, which not only damage the lung structure, but also accelerate the neutrophil inflammatory response [23]. Based on the mechanism of action of azithromycin, it is suggested that the mechanism of acute exacerbation of CB may be due to the existence of multiple neutrophil subtypes.

It was found that FeNO index was significantly elevated in COPD patients with acute exacerbation of CB at the stable stage, when the treatment was ineffective or if acute exacerbation occurred. COPD was considered a disease characterized by inflammation that was accompanied by a predominant infiltration of neutrophils. However, several studies have confirmed the involvement of eosinophils [24] in addition to neutrophils. Eosinophils in the airway increase significantly, particularly during acute exacerbation. There was a positive correlation between FeNO and eosinophils in the airway mucosa. Therefore, the mechanism of acute attack of CB was probably due to the eosinophil type.

Our study revealed that salmeterol-fluticasone combined with tiotropium bromide to treat COPD with acute exacerbation CB could alleviate clinical symptoms without improving the indicators relating to pulmonary functions. This finding was inconsistent with the traditional knowledge that the combination of salmeterol-fluticasone and tiotropium bromide effectively improves pulmonary function. On the contrary, a regimen involving azithromycin was effective in improving clinical symptoms and imaging parameters, and also effectively improved indicators relating to pulmonary function.

The plausible reasons for these findings could be explained as follows: 1. The object selection in this study was different and it focused only on COPD patients with acute exacerbation of CB in the stable stage instead of COPD patients in the exacerbation stage. 2. The sample size of this study was small, which probably led to biased results. 3. Azithromycin could indeed improve the level of pulmonary function in COPD patients with CB in the stable stage. A further investigation with larger sample size and a more deliberate design may be needed to gather sufficient evidence in terms of using azithromycin in different phenotypes of COPD and obtain effective treatment for COPD.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure of conflict of interest

None.

Address correspondence to: Yangfei Lu, Department of Respiratory Medicine, The First People's Hospital of Fuyang Hangzhou, Hangzhou 311400, Zhejiang, China. Tel: +86-13291895705; E-mail: luyangfei1223@163.com

References

[1] Trinkmann F, Saur J, Borggrefe M and Akin I. Cardiovascular comorbidities in chronic obstructive pulmonary disease (COPD)-current considerations for clinical practice. J Clin Med 2019; 8: 69.

[2] Park YB, Rhee CK, Yoon HK, Oh YM, Lim SY, Lee JH, Yoo KH and Ahn JH. Revised (2018) COPD clinical practice guideline of the korean academy of tuberculosis and respiratory disease: a summary. Tuberc Respir Dis (Seoul) 2018; 81: 261-273.

[3] Kling JM and Williams K. Respiratory diseases: sex and gender evidence in obstructive sleep apnea, chronic obstructive pulmonary disease, and asthma. In: Jenkins MR and Newman CB, editors. How sex and gender impact clinical practice. Academic Press; 2021. pp. 289-306.

[4] Jin Z, Han J and Zhang X. Analysis of the efficacy of low-dose azithromycin combined with symbicort on stable COPD. Anhui Med J 2017; 38: 591-594.

[5] Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, Fabbri LM, Goldin JG, Jones PW, Macnee W, Make BJ, Rabe KF, Rennard SI,

Sciurba FC, Silverman EK, Vestbo J, Washko GR, Wouters EF and Martinez FJ. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010; 182: 598-604.

[6] Chen Y. Interpretation of Spanish guidelines for management of chronic obstructive pulmonary disease (GesEPOC) in 2017. Chinese Journal of the Frontiers of Medical 2017; 9: 23-27.

[7] Huo L, Fan X, Lu Z, Wang R and Tang W. Correlation between FeNO and peripheral blood eosinophils and lung function in asthma exacerbations. J Clin Pulm Med 2014; 19: 583-585, 589.

[8] Jiang Z, Huang Y, Jiang H, Wang P, Zhang L, Ren L and Han P. Albuterol combined with tiotropium bromide to improve the conditions and pulmonary functions of patients with acute exacerbation of chronic obstructive pulmonary disease. All Life 2020; 13: 668-674.

[9] Beeh KM, Burgel PR, Franssen FME, Lopez-Campos JL, Loukides S, Hurst JR, Fležar M, Ulrik CS, Di Marco F, Stolz D, Valipour A, Casserly B, Ställberg B, Kostikas K and Wedzicha JA. How do dual long-acting bronchodilators prevent exacerbations of chronic obstructive pulmonary disease? Am J Respir Crit Care Med 2017; 196: 139-149.

[10] Martinez-Garcia MA, Aksamit TR and Agusti A. Clinical fingerprinting: a way to address the complexity and heterogeneity of bronchiectasis in practice. Am J Respir Crit Care Med 2020; 201: 14-19.

[11] Conickx G. Role of microRNAs in the pathogenesis of chronic obstructive pulmonary disease (COPD). Ghent University 2017.

[12] Agusti A. The path to personalised medicine in COPD. Thorax 2014; 69: 857-864.

[13] Wouters EF, Wouters BB, Augustin IM and Franssen FM. Personalized medicine and chronic obstructive pulmonary disease. Curr Opin Pulm Med 2017; 23: 241-246.

[14] Camiciottoli G, Bigazzi F, Paoletti M, Cestelli L, Lavorini F and Pistolesi M. Pulmonary function and sputum characteristics predict computed tomography phenotype and severity of COPD. Eur Respir J 2013; 42: 626-635.

[15] Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 2008; 372: 1107-1119.

[16] Brandsma CA, Van den Berge M, Hackett TL, Brusselle G and Timens W. Recent advances in chronic obstructive pulmonary disease pathogenesis: from disease mechanisms to precision medicine. J Pathol 2020; 250: 624-635.

[17] Rogliani P, Ritondo BL, Laitano R, Chetta A and Calzetta L. Advances in understanding of mechanisms related to increased cardiovascular risk in COPD. Expert Rev Respir Med 2021; 15: 59-70.

[18] Vázquez-Laslop N and Mankin AS. How macrolide antibiotics work. Trends Biochem Sci 2018; 43: 668-684.

[19] Vermeersch K, Gabrovska M, Deslypere G, Demedts IK, Slabbynck H, Aumann J, Ninane V, Verleden GM, Troosters T, Bogaerts K, Brusselle GG and Janssens W. The belgian trial with azithromycin for acute COPD exacerbations requiring hospitalization: an investigator-initiated study protocol for a multicenter, randomized, double-blind, placebo-controlled trial. Int J Chron Obstruct Pulmon Dis 2016; 11: 687-696.

[20] Wang C, Zhou J, Wang J, Li S, Fukunaga A, Yodoi J and Tian H. Progress in the mechanism and targeted drug therapy for COPD. Signal Transduct Target Ther 2020; 5: 248.

[21] Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Jenkins C, Peters MJ, Marks GB, Baraket M, Powell H, Taylor SL, Leong LEX, Rogers GB and Simpson JL. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 2017; 390: 659-668.

[22] Khalaf RM, Lea SR, Metcalfe HJ and Singh D. Mechanisms of corticosteroid insensitivity in COPD alveolar macrophages exposed to NTHi. Respir Res 2017; 18: 61.

[23] Nicholson TT, Franciosi A, Landers S and Butler MW. Assessing potential risks of treatment with long-term azithromycin in COPD patients: long-term oxygen users beware? Ir J Med Sci 2016; 185: 993-997.

[24] Brightling CE. Biomarkers that predict and guide therapy for exacerbations of chronic obstructive pulmonary disease. Ann Am Thorac Soc 2013; 10 Suppl: S214-9.