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# Clinical efficacy of sequential therapy with voriconazole on COPD patients in acute phase with pulmonary aspergillosis and effects on cytokines and pulmonary functions

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**Abstract. – OBJECTIVE: To explore the clinical efficacy of sequential therapy with voriconazole on chronic obstructive pulmonary disease (COPD) patients in acute phase with pulmonary aspergillosis and its effects on cytokines and pulmonary functions.**

**PATIENTS AND METHODS: A total of 110 COPD patients in acute phase with pulmonary aspergillosis who were admitted to the hospital between February 2015 and November 2016 were enrolled. We divided them randomly into two groups, i.e., the control group (n = 55) and the treatment group (n = 55). Patients in the control group took itraconazole capsules orally (200 mg/time, twice per day for three days followed by once per day). Patients in treatment group underwent sequential treatment with voriconazole through intravenous infusion at a dose of 5 mg/kg/time twice a day for 3 days followed by a dose of 4 mg/kg/time, twice a day for 8 days. Then, patients took voriconazole orally at a dose of 150 mL/time, twice a day for 6 days. Patients in two groups received the treatment for a total of 14 days. After treatment, we evaluated the levels of tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and IL-8. The total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLco), and arterial oxygen saturation ($SaO_2$), were measured as well.**

**RESULTS: The total effectiveness rates of the treatment group and the control group were 83.63% and 61.82%. The differences had statistical significance ($p < 0.01$). After treatment, the incidence of chest pain, cough, sputum-coughing, hemoptysis, cyanosis, and dyspnea in the treatment group was significantly fewer than that in the control group ($p < 0.05$). TCL, DLco, and SaO2 in the two groups were significantly ameliorated by treatment ($p < 0.05$). The amelioration in the treatment group was more prominent than that in the control group ($p < 0.05$). The levels of TNF-α, IL-8, and IL-6 in the two groups were decreased dramatically by the treatments. The decrease in the treatment group was significantly lower than those in the control group ($p < 0.05$). Occurrence of adverse reactions in treatment group and control group were 8.33% and 6.25%, respectively; ($p > 0.05$).**

**CONCLUSIONS: Sequential therapy with voriconazole exhibits promising clinical efficacy in COPD patients in acute phase with pulmonary aspergillosis. The treatment ameliorated the clinical symptoms and vital signs of patients significantly. It also improved the pulmonary functions and inhibited the inflammatory responses of patients with evident clinical efficacy.**

*Key Words:*
Voriconazole, Itraconazole capsule, Sequential therapy, COPD, Pulmonary aspergillosis.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic irreversible disease severely affecting the survival rate of middle-aged and elder population. With an increasing tendency in incidence rate, COPD usually causes insufficiency of nutrition, immune defects or any other complications, even death[1]. Decline in immune functions of patients usually leads to the opportunistic infections by fungus like aspergillus in the respiratory system. When the infection takes place in the acute phase of COPD, it will further aggravate the COPD condition and induce the systemic

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reactions, including a variety of complications, or even death in patients[2,3]. Regular symptomatic treatment, as a kind of conventional treatment strategy, can prevent the infection by administration of antibiotics, which, however, usually gain poor efficacy with evident adverse reactions. Voriconazole, the 3rd broad-spectrum antibiotic, has been considered as the best option in the treatment of many fungal infections[4] and has been widely applied in clinical practices. Promising efficacy has gained in the treatment of COPD patients in acute phase with pulmonary aspergillosis through sequential therapy with voriconazole.

## Patients and Methods

### Patients

All subjects were COPD patients in acute phase with pulmonary aspergillosis. They were admitted to the hospital for treatment between February 2015 and November 2016. There were 51 males and 59 females aged between 41 and 77 years old with an average of (56.8 ± 0.7) years. Their disease course ranged from 1 to 12 years. The enrollment of subjects was in strict accordance with the diagnostic criteria of COPD and pulmonary aspergillosis[5]. The local Ethical Committee approved this study. All patients signed the written informed consents.

### Exclusion Criteria

Patients with pulmonary diseases caused by other factors, like interstitial pneumonia, bronchogenic carcinoma, or acute respiratory distress syndrome; patients with symptoms of organ failure; patients who had taken drugs that were similar or opposite to those in this study.

### Grouping Criteria

All patients were divided randomly into control group (n=55) and treatment group (n=55). In the treatment group, there were 27 males and 28 females aged between 41 and 77 years old with an average of (56.2 ± 0.3) years old. In control group, there were 24 males and 31 females aged between 43 and 76 years old with an average of (57.4 ± 0.8) years. Comparison of data like age, occupation, disease history and length of stay in hospital of patients in two groups showed that there were no statistically significant differences, suggesting that data between the two groups were comparable.

## Methods

### Control Group

After admission, patients underwent symptomatic support treatment, including bronchodilators, glucocorticoid, and oxygen therapy in the family to maintain the normal physiological function. Patients in control group took itraconazole capsules [SFDA No. Z230201; 100 mg/capsule; manufactured by Hasen-modern (Shanghai, China) Pharmaceuticals Co., Ltd., Shanghai, China] at a dose of 200 mg/time and twice per day for three days, followed by once per day.

### Treatment Group

On the basis of symptomatic treatment, patients in treatment additionally underwent sequential therapy with voriconazole in the following procedures: intravenous infusion of voriconazole (SFDA No. X20010392; 200 mg/bottle; manufactured by Sichuan Medco Huakang Pharmaceutical Co., Ltd., Chengdu, Chia) at a dose of 6 mg/kg/time, twice a day for 3 days followed by 4 mg/kg/time, twice a day for 8 d. Thereafter, patients took voriconazole tablet orally (SFDA No. W20020413; 50 mg/tablet; manufactured by Chengdu Huasun Group Co., Ltd., Chengdu, China) at a dose of 150 mg/time, twice per day for a total of 6 days. Treatment for patients in two groups lasted for two weeks, during which vital signs of patients were monitored closely. Any adverse reaction would be the sign for immediate adoption of drug withdrawal.

### Observation Indicators and Detection Methods

Levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-8 in serum were measured by the enzyme-linked immunosorbent assay (ELISA) (BGI, Shanghai, China). Clinical indicators including total lung capacity (TCL), diffusing capacity of the lung for carbon monoxide (DLco), and arterial oxygen saturation ($SaO_2$) were recorded. Indicators of ameliorating in clinical symptoms that were observed in this study included chest pain, cough and sputum-coughing, hemoptysis, cyanosis, and dyspnea. Comprehensive analysis was performed to figure out the effect on amelioration of patients' symptoms with a high specificity. Specifically, these indicators referred to: the degree, feature, and cause of chest pain; feature and frequency of a cough with or without sputum and the characteristics of sputum (if any); hemoptysis and the amount of blood; cyanosis; dyspnea and its cause.

### Evaluation of Efficacy

The criteria of cure: patients with no symptoms, normal results of auxiliary examinations, and overall recovery. The criteria of effectiveness: patients with no symptoms and basic recovery but an anomaly in laboratory examination or bacteriological analysis. The criteria of improvement: patients with some amelioration in symptoms, the presence of pathogens in auxiliary examinations and partial recovery. The criteria of ineffectiveness: patients with no improvement, or even aggravations in symptoms or results in auxiliary examinations[6].

Total effectiveness rate = (cure + effective + improved)/number of total cases.

### Adverse Reactions

During treatment, adverse reactions, including nausea, vomiting, fever, respiratory distress or rage, were observed in patients of two groups.

### Statistical Analysis

SPSS 20.0 software (IBM, Armonk, NY, USA) was applied for the statistical analysis of data. Measurement data were presented as mean ± standard deviation ($\bar{x} \pm s$), *t*-test was adopted for comparison, while $x^2$-test for comparison of enumeration data. $p < 0.05$ suggested that the difference had statistical significance.

## Results

### Comparison of Clinical Efficacy Between Two Groups

After treatment, there were 18 cure cases, 18 effective cases, and 10 improved cases in the treatment group. The total effectiveness rate was 83.63% in the treatment group. In the control group, there were 10 cure cases, 9 effective cases, and 15 improved cases; the total effectiveness rate was 61.82%. The difference in total effectiveness rates between two groups showed statistical significance ($p < 0.01$; Table I).

### Comparison of the Improvement Indicators in Clinical Symptoms Between the Two Groups

After treatment, the cases of chest pain, cough and sputum-coughing, hemoptysis, cyanosis and dyspnea in the treatment group were significantly fewer than those in the control group. The differences had statistical significance ($p < 0.05$; Table II).

### Comparisons of TCL, DLco, and $SaO_2$ Before and After Treatment Between the Two Groups

After treatment, indicators like TCL, DLco, and $SaO_2$ in two groups were significantly improved in comparison with those before treatment ($p < 0.05$). The amelioration in the treatment group was more prominent than that in the control group ($p < 0.05$; Table III).

### Comparison of the Levels of Cytokines Before and After Treatment Between the Two Groups

The levels of TNF-α, IL-8, and IL-6 in two groups after treatment were all decreased dramatically in comparison with the levels before treatment ($p < 0.01$). Those levels in the treatment group were significantly lower than those in the control group ($p < 0.01$ or 0.05; Table IV).

### Adverse Reaction

Prevalence rates of adverse reactions in the treatment group and the control group were 8.33% and 6.25%. The difference had no statistical significance ($p > 0.05$).

## Discussion

Acute-phase COPD complicated with pulmonary aspergillosis has been regarded as a complex disease with severe conditions in clinical practices[7,8]. For years its incidence and mortality rates have been increasing. Various factors are involved in the incidence of COPD, which can

**Table I.** Comparison of clinical efficacy between two groups.

| Group | Case (n) | Cure (n) | Effective (n) | Improved (n) | Ineffective (n) | Total effectiveness rate (%) |
|---|---|---|---|---|---|---|
| Treatment group | 55 | 18 | 18 | 10 | 9 | 83.63** |
| Control group | 55 | 10 | 9 | 15 | 21 | 61.82 |

*Note*: **$p < 0.01$ *vs*. control group.

**Table II.** Comparison of the improvement indicators in clinical symptoms between two groups.

| Group | Chest pain (n) | Cough and sputum-coughing (n) | Hemoptysis (n) | Cyanosis (n) | Dyspnea (n) |
|---|---|---|---|---|---|
| Treatment group | 9* | 10* | 8* | 9* | 7* |
| Control group | 16 | 21 | 25 | 29 | 22 |

*Note*: **$p < 0.05$ *vs*. control group.

**Table III.** Comparisons of TCL, DLco, and $SaO_2$ before and after treatment between two groups.

| Group | TCL (measured/predicted %) | | DLco (measured/predicted %) | | $SaO_2$ (measured/predicted %) | |
|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Treatment group | 54.59 ± 4.22 | 70.27 ± 6.80[a] | 54.70 ± 5.19 | 68.83 ± 4.82[a] | 74.70 ± 7.99 | 96.22 ± 6.87[a] |
| Control group | 55.35 ± 4.38 | 62.72 ± 6.29[b] | 54.72 ± 5.25 | 61.38 ± 4.27[b] | 75.17 ± 7.25 | 91.99 ± 6.02[b] |
| *t* | 0.0298 | 9.873 | 0.0392 | 7.982 | 0.0193 | 4.917 |
| *p* | 0.9817 | 0.0001 | 0.9619 | 0.0006 | 0.9109 | 0.0016 |

*Note*: [a]$p < 0.01$ and [b]$p < 0.05$ *vs*. before treatment.

**Table IV.** Comparison of the levels of cytokines before and after treatment between two groups.

| Group | TNF-α | | IL-8 | | IL-6 | |
|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Treatment group | 48.60 ± 8.22 | 40.27 ± 6.80[a] | 48.70 ± 5.19 | 38.83 ± 4.88[a] | 114.70 ± 10.99 | 100.22 ± 6.88[a] |
| Control group | 48.35 ± 8.19 | 44.72 ± 7.29[b] | 48.72 ± 5.25 | 44.38 ± 4.22[b] | 112.95 ± 10.25 | 109.99 ± 7.03[b] |
| *t* | 0.1373 | 2.9663 | 0.0777 | 2.8826 | 0.0803 | 5.7297 |
| *p* | 0.8917 | 0.0032 | 0.9382 | 0.0057 | 0.893 | 0.0002 |

*Note*: [a]$p < 0.01$ and [b]$p < 0.05$ *vs*. before treatment.

lead to cough and sputum-coughing, cyanosis, dyspnea, chest pain as well as dysfunction in nutrient absorption, defect in immune system and decline in immune functions. These will finally induce the secondary opportunistic infections, in which fungal infection (mainly the aspergillus) is the most frequent event. Clinical manifestations include abuse of antibiotics and steroids and insufficiency of nutrients. As a consequence, the COPD patients usually suffer from poor prognosis and an extremely high mortality rate. Oral administration of itraconazole has been used for treating acute-phase COPD complicated with pulmonary aspergillosis. However, it shows poor clinical efficacy with slow onset and a variety of complications[9]. Voriconazole is expected to substitute the itraconazole for treatment of this disease. Voriconazole, a broad-spectrum antifungal agent with the modified internal structure of fluconazole, is featured for its broad spectrum, rapid onset, evident efficacy, and slight adverse reaction. It was preferred in the treatment of most of the fungal infection in clinical practices. The basic mechanism is that it can inhibit the metabolism of ergosterol, thereby blocking the transcription and translation of DNA in fungus and leading to the disinfection of fungus. Due to its biologic specificity in action target, it produces little effect on normal tissues and cells[10-12]. From a variety of aspects, including symptoms, vital signs, auxiliary examination, and cytokines of patients, we evaluated the clinical efficacy on

COPD patients in the two groups. The application of voriconazole in the form of sequential therapy can adjust the dose and administration according to the stage of treatment. This will increase the efficiency and avoid the adverse reaction. TNF-α can induce inflammation and cytokines that regulate the immune system[13]. TNF-α in high expression can increase the ratio of leukocytes, especially the neutrophils, thereby inducing the onset of inflammatory responses, and damaging the bronchus and airway. IL-8 originated from inflammatory cells like alveolar macrophage, lymphocyte, and neutrophils, with a strong chemotactic effect on other inflammatory cells, and it is subjected to the chemotactic effect of neutrophils, which can activate and induce its effect in inflammatory sites[14]. IL-6 has a synergistic effect on IL-8 through the same signal pathway, and is heavily secreted after inflammatory hyperplasia. It can promote the differentiation of Th2 cells through feedback pathway. Also, it shows a cytotoxic effect on T-lymphocytes. Results in our research showed that the levels of TNF-α, IL-8, and IL-6 after treatment in two groups were significantly decreased in comparison with the levels before treatment. The decreases in the treatment group were more prominent than those in the control group, suggesting that sequential therapy with voriconazole can regulate the immune functions of patients effectively. Besides, we also found that after sequential therapy with voriconazole, a significant improvement was identified in indicators of pulmonary functions (TCL, DLco and $SaO_2$) in two groups in comparison with those before treatment ($p < 0.05$). The improvement in the treatment group was much better than that in the control group ($p < 0.01$), indicating that standardized therapy with voriconazole can ameliorate the pulmonary functions of COPD patients in acute phase with pulmonary aspergillosis.

## Conclusions

Sequential therapy with voriconazole exhibits promising clinical efficacy on COPD patients in acute phase with pulmonary aspergillosis. The treatment could not only ameliorate the clinical symptoms and vital signs of patients significantly, but also improve their pulmonary functions and inhibit their inflammatory responses. Thus, it is worthy of promoting the treatment in clinical practice.

### Ethical Committee Approval

The research was conducted in accordance with the Declaration of Helsinki and the United National Institutes of Health.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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