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Efficacy of Itraconazole in the Treatment of Patients with Chronic Cough Whose Sputa Yield Basidiomycetous Fungi—Fungus-Associated Chronic Cough (FACC)

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ORIGINAL ARTICLE

Efficacy of Itraconazole in the Treatment of Patients with Chronic Cough Whose Sputa Yield Basidiomycetous Fungi—Fungus-Associated Chronic Cough (FACC)

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Objectives. This controlled study was performed to clarify the therapeutic benefit of itraconazole for the treatment of patients with chronic cough, wherein a sputum culture yielded basidiomycetous (BM) fungi. **Methods.** Of the 171 patients who visited our hospital for the diagnosis and treatment of chronic cough, BM was detected in the sputum of 39 patients. Informed consents were obtained from 21 patients who were subsequently enrolled in this trial. After the administration of the standard therapy, all the patients were enrolled in a randomized placebo-controlled study with 2 weeks of treatment with a low dose of itraconazole (50 mg/day) ($n = 10$) in comparison with a corresponding period of treatment with matched placebo (ambroxol hydrochloride 45 mg/day) ($n = 11$). Coughing was assessed using subjective cough symptom scale and capsaicin cough challenging. **Results.** The treatment with itraconazole, but not placebo ($p = 0.17$), was associated with a significant improvement in the cough scale ($p = 0.0051$); moreover, the improvement achieved with itraconazole was significant ($p < 0.001$) when compared with that of the placebo. **Conclusions.** Low-dose itraconazole was shown to be an effective antitussive in patients with chronic cough in which sputum examination yielded BM fungi. The 21 patients described here entailed the following manifestations: (1) chronic cough; (2) the presence of environmental fungi, particularly basidiomycetous (BM) fungi, in the sputum; and (3) good clinical response to antifungal drugs. These clinical features may constitute a unique disease concept called fungus-associated chronic cough (FACC).

Keywords antifungal drugs, basidiomycetous fungi, chronic cough, fungus-associated chronic cough (FACC), Itraconazole

INTRODUCTION

Many studies have reported the pathophysiological features of allergic airway disorders (1–3), which present as chronic cough; however, only a few studies, including our case reports (4, 5), have demonstrated the etiological agents involved in these disorders. After our previous report on a typical case of chronic cough with sputum eosinophilia caused by an allergic reaction to basidiomycetous fungi (BM) (6, 7), we have focused on the possible role of BM as a fungal aeroallergen (8). Since BM fungi are rarely detected in the culture of pharyngeal swabs obtained from non-coughers (9, 10), and the positive ratio of the immediate subcutaneous reaction for BM fungi in allergic airway diseases such as atopic cough (AC) (11–13), cough-variant asthma (CVA) (14), and cough-predominant asthma was significantly higher than that in non-coughers (unpublished data), we consider that the positive culture results were not caused by an environmental

fungal contamination. Therefore, we have hypothesized that BM fungi colonizing in the pharynx or lower respiratory tract play an important role in allergic airway disorders.

Although we have reported the efficacy of antifungal drug therapies in atopic cough in which sputum examination yielded BM fungi [15, 16], there are few clinical trial data to support the efficacy. The present controlled study was performed to clarify the therapeutic benefits of itraconazole in patients with fungus-associated chronic cough (FACC).

METHODS

Patients

From April 2005 to May 2006, 171 patients visited our hospital for the diagnosis and treatment of chronic cough, which was defined as isolated persistent cough lasting 8 weeks or more. BM fungi were detected in the sputa of 39 of the 171 patients (22.8%). Of these 39 patients, informed consents were obtained from 21 patients, and those consenting patients were subsequently enrolled in this study. This randomized, single-blinded, placebo-controlled, parallel-group trial was approved by the institutional review boards (reference 2005005), and approval for the study was obtained from UMIN-CTR (reference R000000432; Umin000000114).

H.O. Y.T., and K.M. belong to the Fungus Association Cough Research Society. Y.T. and K.M. contributed in the identification of fungi. M.F. was the general conductor of this study.

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The cause of chronic cough in each patient was diagnosed based on a questionnaire, blood examination findings, chest and sinus radiographs, induced-sputum examination, pulmonary function tests [17], test for cough reflex sensitivity to inhaled capsaicin [18], bronchial reversibility in response to bronchodilators, bronchial responsiveness to methacholine [19], and the efficacy of individual cause-specific treatments.

Capsaicin cough threshold was measured as an index of airway cough reflex sensitivity according to the method reported by the authors [18] at the first visit and after each therapy. The capsaicin cough threshold was defined as the lowest concentration of inhaled capsaicin eliciting five or more coughs. Positive bronchial reversibility was defined as percentage increase in forced expiratory volume in 1 second (FEV_1) > 12% and absolute increase in FEV_1 > 200 mL. The non-specific bronchial responsiveness to methacholine was assessed according to the method described by Cockcroft et al. [19]. The results were expressed as the provocation concentration (mg/mL) required to cause a 20% or more decrease from the baseline FEV_1 (respiratory threshold of methacholine; RT-Meth).

The examinations were performed in accordance with the diagnostic criteria for each cause, as recommended by the Japanese Cough Research Society [20] and Japanese Respiratory Society [21]. The clinical features of AC [11] were considered to be as follows: (1) chronic bronchodilator-resistant nonproductive cough with "tickle" in the throat lasting for more than 8 weeks; (2) absence of wheezing, dyspnea, hemoptysis, or pleurisy, and no adventitious lung sounds on physical examination; (3) presence of one or more global atopic findings, including past history and/or complication of allergic diseases except for bronchial asthma, family history of allergic diseases, peripheral blood eosinophilia, elevated total immunoglobulin E (IgE) level in the serum, positive specific IgE antibody to common aeroallergens, and positive allergen skin test; (4) presence of eosinophils in hypertonic saline-induced sputum and/or submucosa of trachea and/or bronchi that had undergone biopsy; (5) normal FEV_1 , forced vital capacity (FVC), and FEV_1 /FVC ratio; (6) no bronchial reversibility defined as less than a 5% increase in FEV_1 after inhalation of 300 μ g salbutamol following 250 mg aminophylline injection; (7) bronchial responsiveness within normal limits; (8) increased airway cough reflex sensitivity; and (9) complete relief of the cough upon treatment with histamine H1-antagonists and/or corticosteroid therapy.

CVA was diagnosed based on the following diagnostic criteria [14]: (1) chronic non-productive cough as an isolated symptom lasting for more than 8 weeks; (2) absence of a history of wheezing or dyspnea, and no adventitious lung sounds on physical examination; (3) absence of post-nasal drip (PND) to account for the cough; (4) normal limits of FEV_1 , FVC, and FEV_1 /FVC ratio; (5) presence of bronchial hyper-responsiveness (RT-Meth < 10 mg/mL); (6) normal limits of cough reflex sensitivity ($C5$ > 3.9 μ m); (7) no abnormal findings indicative of cough etiology on chest radiograph; and (8) relief of cough with bronchodilator therapy. When all criteria were satisfied, a definite diagnosis of CVA was made.

Sinobronchial syndrome (SBS) [22] was diagnosed according to the following diagnostic criteria: (1) productive cough without wheezing lasting for 8 weeks or more; (2)

one or more of the following findings: (a) symptoms such as PND and throat clearing; (b) signs such as mucus or mucopurulent secretion in the upper and middle pharynx, and cobble stone appearance of the mucosa; (c) fluid retention or mucosal thickening on sinus radiograph or computed tomographic (CT) scan; and (d) increased neutrophils without eosinophils in nasal secretions and spontaneous sputum; (3) no atopic findings; (4) no bronchial reversibility; (5) bronchial responsiveness within normal limits; (6) normal limits of cough reflex sensitivity; and (7) relief of cough on treatment with 14- or 15-member macrolides.

Assessment of the Efficacy of Treatment of Cough Symptoms

The efficacy of cough treatment was assessed with a subjective cough symptom scale (SCSS). It was assumed that the sum sensation regarding the intensity and frequency of coughs in the 1-week period before the first visit was recorded as 10 points, and the complete absence of cough was recorded as 0 points. The points on the cough scale were recoded for each patient during each visit. The efficacy of the treatment was evaluated on the basis of the change in the cough scale before and after the treatment (Δ cough scale): 10 to 8 points was regarded as excellent; 7 to 5 points as good; 4 to 3 points as fairly good; and 2 to 0 points as unsatisfactory.

Study Design for the Treatment of Chronic Cough

All patients were administered the standard therapy, which involved administration of bronchodilators for the first 7 days (a combination of oral 40 μ g/day clenbuterol and salbutamol inhalation at bed and/or when required) and administration of histamine H1-antagonists and inhaled corticosteroids (a combination of 10 mg/day cetirizine hydrochloride and 400 μ g/day fluticasone propionate) for the next 7 days. Subsequently, the patients were randomly assigned to receive either 50 mg/day (low-dose) itraconazole or 45 mg/day ambroxol hydrochloride (placebo) for 2 weeks (trial phase).

Patients who completed the above-mentioned study were given the option of participating in a 2-week extension of the study and were given itraconazole when their cough had not been adequately controlled during the core study.

Strain Isolations and Morphological Observations

Sputum samples obtained from the patients were inoculated on Sabouraud's dextrose agar (SDA) containing chloramphenicol. The morphological features of the strains were recorded by a mycological specialist by using the slide culture method (30°C for 2 weeks) and by staining with lactophenol cotton blue.

Statistical Analysis

The subjective cough symptom scale SCSS was compared between the itraconazole and the placebo groups by using the Mann-Whitney *U* test. The change in the cough scale within the group was analyzed using the Wilcoxon signed-rank test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Clinical Findings and Diagnosis of Chronic Cough

The patients with chronic cough comprised 11 males and 10 females with chronic cough (4 males and 6 females in the itraconazole group, and 7 males and 4 females in the control group) with mean age of 51.9 ± 14.2 (SD) years (49.6 ± 18.4 (SD) years in the itraconazole group, and 54.0 ± 9.5 (SD) years in the control group). The gender and age values were not significantly different between the two groups. Chest and sinus radiographs were normal for all the patients. Atopic tendency, such as pollen was recognized in 5 patients (patient 1, 4, 11, 15, and 21). Three patients in the control group were current smokers; and only 1 patient was an ex-smoker in the itraconazole group. No significant difference was observed in the mean duration of cough symptoms before the first visit between the two groups (8.2 ± 18.2 [SD] months in the itraconazole group and 4.7 ± 4.7 [SD] months in the control group).

The total serum IgE levels were found to be elevated in 3 patients (1 in the itraconazole group and 2 in the control group). Of the 15 patients in whom adequate induced sputum was obtained by inhalation of hypertonic saline, sputum eosinophilia was observed in 5 patients (1 in the itraconazole group and 4 in the control group).

Chronic airflow limitation was considered present when the ratio of FEV₁ to FVC (FEV₁/FVC ratio) was <0.7 . Further, FEV₁ of $<80\%$ of the predicted value was found in 2 of the 21 patients. Positive bronchial reversibility was not observed in any patients. Cough reflex sensitivity [18] was increased in 8 patients. Bronchial responsiveness to methacholine [19] was exaggerated in 4 patients. Of the 21 patients enrolled in this study, 10 were randomly assigned to the itraconazole group and 11 to the active placebo group (control group). No clinically important demographic differences were observed between the two groups. No patient withdrew from the study (Table 1).

Effect of Each Therapy

During the first treatment phase, the bronchodilator therapy showed a partial effect in 3 patients (patients 1, 12, and 21). During the second treatment phase, histamine H1 antagonists and inhaled corticosteroids produced a partial response in 4 patients (patients 6, 10, 14, and 15). None of the patients were completely relieved of their cough after these treatments. During the trial phase, no patient in the control group experienced relief from cough. However, the antifungal therapy was remarkably efficacious in relieving coughing in 10 patients in the itraconazole group; the result was excellent in 3 patients (patients 3, 6, and 7) and good in 7 patients (patients 1, 2, 4, 5, 8, 9, and 10).

No significant difference was observed in the subjective cough symptom scale SCSS between the two groups before the trial phase. The treatment with itraconazole, but not placebo ($p = 0.17$), was associated with a significant improvement in the cough scale ($p = 0.0051$); moreover, the improvement achieved with itraconazole was significant ($p < 0.001$) when compared with that achieved with the placebo (Figure 1). Individual changes in the cough scale before and after the tested treatments are shown in Figure 2.

Except for patient 2, none of the patients in the itraconazole group revealed deterioration in airway cough reflex sensitivity to capsaicin after the 2-week itraconazole trial, whereas only 1 patient of 11 in the control group demonstrated improvement in the cough threshold (Figure 3). As a group, the cough threshold tended to increase in the itraconazole group ($p = 0.0747$) but did not in the control group ($p = 0.1380$) as shown in Figure 3.

After the trial period, all the patients in the control group were administered 50 mg/day of itraconazole for 14 days as an extension study, after which they exhibited a clinical response with a significant decrease in the SCSS. Consequently, none of the patients were treated with a high dose of proton-pump inhibitors for suspected GER [23]. When we

TABLE 1.—Characteristics of the patients studied

	Age	Gender	Smoking B1	Duration of cough (M)	IgE (U/ml)	Sputum Eo (%)	%FVC	%FEV1	FEV1%	RT-Meth (μ g/ml)	Bronchial reversibility (%)	Cough threshold (μ M)
ITZ												
1	66	F	non	2	628	ND	113.2	109.4	72.1	5000	8.6	1.95
2	64	F	non	2	72	ND	118.8	110.5	73.9	ND	1.9	1.95
3	40	M	EX	3	228	ND	94.9	78.8	74.6	20000	2.2	31.3
4	67	F	non	60	8	0	104.5	115.4	80.3	20000	1.6	0.98
5	28	M	non	5	48	0	125.0	113.0	86.6	20000	4.7	3.91
6	20	M	non	2	893	1	135.6	123.9	88.8	20000	3.2	3.91
7	66	F	non	2	ND	ND	104.5	130.6	90.1	20000	2.2	0.98
8	34	M	non	2	34	0	118.7	118.7	93.1	20000	2.1	0.98
9	45	F	non	2	56	ND	109.5	112.0	93.0	20000	2.1	3.91
10	66	F	non	2	94.3	17	128.7	126.6	77.0	20000	4.7	0.49
MUC												
11	68	M	8×12	2	229	2	94.7	103.1	76.9	20000	−0.4	31.3
12	39	M	non	2	238	0	106.9	103.4	86.4	1250	−1.4	31.3
13	58	F	non	12	145	54	135.5	120.5	72.6	5000	7.8	3.91
14	47	F	non	2	153	3	140.1	120.0	77.2	20000	2.7	3.91
15	58	M	20×35	12	70	2	137.0	105.4	66.9	20000	−0.6	1.95
16	58	M	25×40	12	ND	11	107.1	89.0	66.3	20000	6.8	0.49
17	50	M	non	2	68	ND	100.0	95.0	83.1	20000	−2.3	1.95
18	44	M	non	2	47	37	117.8	101.7	77.9	20000	7.6	0.98
19	58	F	non	2	15	7	131.4	147.6	88.1	5000	0.4	0.49
20	46	M	non	2	55	3	126.9	120.7	83.3	20000	2.0	0.98
21	68	F	non	2	8	0	152.9	154.5	80.2	20000	2.7	1.95

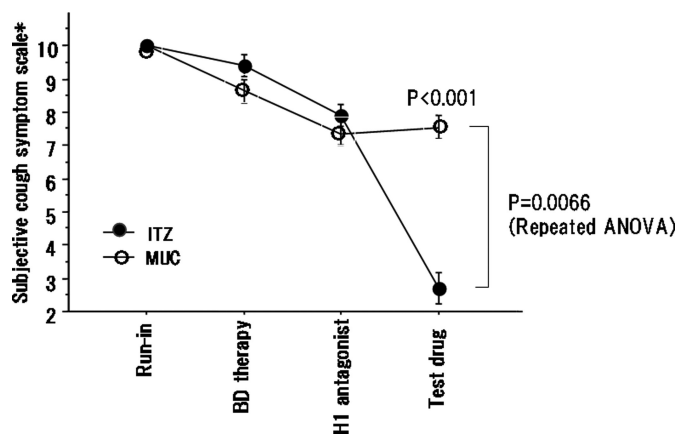


FIGURE 1.—Change in subjective cough symptom scale in each treatment. *It was assumed that the sum sensation regarding the intensity and frequency of coughs in the 1-week period before the first visit was recorded as 10 points, and the complete absence of cough was recorded as 0 points. The points on the cough scale were recorded for each patient during each visit.

finished itraconazole treatment with the result of the improvement of cough symptoms, we confirmed successful eradication of BM fungi in all 11 patients in whom the expectoration was able to be obtained.

DISCUSSION

Although only a limited number of reports in the literature have documented infectious diseases caused by BM fungi, such as *Schizophyllum commune* [24], the *Coprinus* species [25], and allergic bronchopulmonary mycosis [26], much of

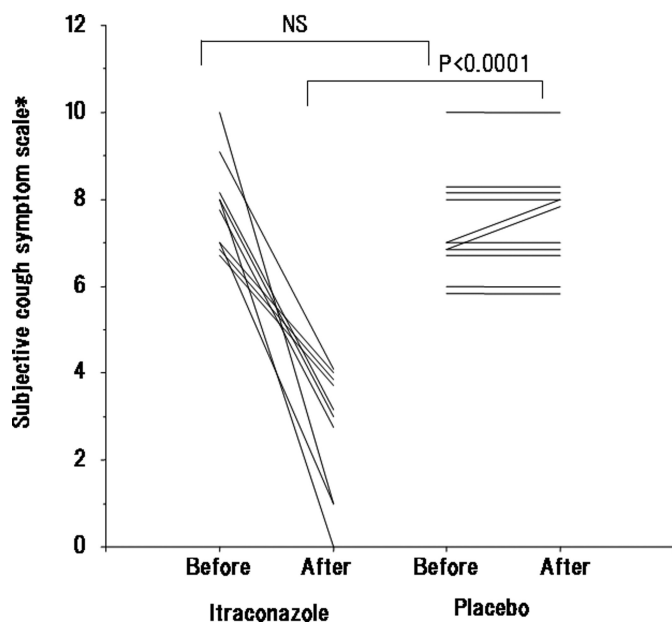


FIGURE 2.—Individual changes in subjective cough symptom scale before and after the tested treatments.* It was assumed that the sum sensation regarding the intensity and frequency of coughs in the 1-week period before the first visit was recorded as 10 points, and the complete absence of cough was recorded as 0 points. The points on the cough scale were recorded for each patient during each visit.

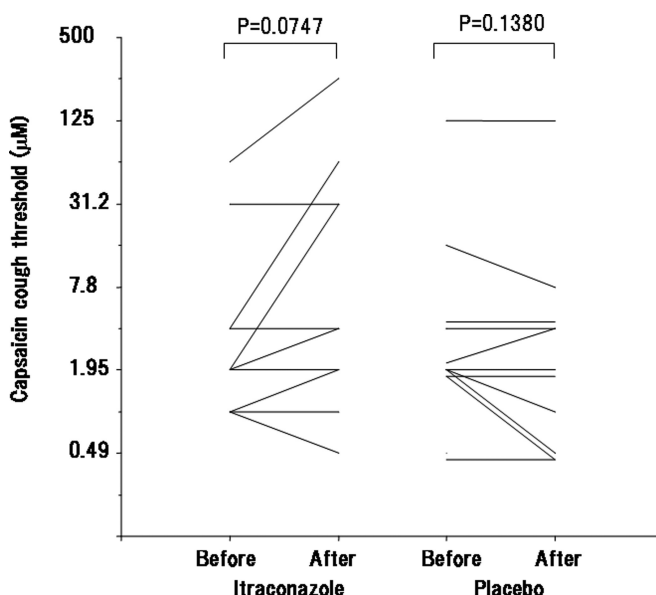


FIGURE 3.—Cough reflex sensitivity to inhaled capsaicin before and after the tested treatments.

the literature reports the possible role of basidiospores as airborne allergens [8]. From the results of our series of studies, we have hypothesized that BM fungi colonizing in the pharynx or lower respiratory tract plays an important role in chronic cough. We have encountered several patients who presented with chronic intractable cough; their sputum examination yielded environmental fungi (particularly BM fungi), and they clinically responded to anti-fungal drug therapies [15, 16]. The present controlled study was performed to clarify the therapeutic benefits of itraconazole in patients with fungus-associated chronic cough.

Regarding the study design, we first evaluated asthmatic components based on the response to bronchodilators, and next we evaluated components of atopic cough based on the responses to histamine H1-antagonists and inhaled corticosteroids. Because it is well-known that gastroesophageal reflux (GER)-associated cough and PND-induced cough are very rare in Japan [27, 28], we decided to perform exclusion of GER-associated cough in the final stage of the treatment. In other words, we decided to use proton-pump inhibitors when the itraconazole treatment failed.

Although the 21 patients who enrolled in this study were randomly assigned to two groups according to the identification number of each patient, the patients in the control group demonstrated more severe airway obstruction compared to those in the itraconazole group. This result may be explained by the fact that the control group contained many smokers; however, no significant difference was seen in mean age and FEV₁/FVC ratio between the two groups.

A definite diagnosis could not be established in any of the 21 patients at the previous stage before the trial phase started because the standard therapies for CVA and AC did not relieve the cough enough in any patients. When we tried to apply them to an existing diagnosis according to extensive diagnostic evaluation and numerous treatment guidelines [20, 21, 23], we barely achieved diagnosis of probable CVA [14]

in 2 patients (patients 1 and 12); based on the result of partial response to bronchodilators with heightened bronchial responsiveness to methacholine, and probable AC [11] in 2 patients (patients 10 and 16); and based on the partial response to the combination of histamine H1-antagonists and inhaled corticosteroids, increased cough reflex sensitivity, and some atopic tendency. Thus, the remaining 17 patients were diagnosed as unknown etiology.

There is no standard therapeutic plan concerning the amount and a period of treatment with antifungal drugs for chronic cough. We decided to carry out a low-dose use of anti-fungal drugs and fixed a treatment period at 2 weeks, based on our previous treatment experience [15, 16]. In the present study, we used SCSS as described in the methods section to evaluate change in cough symptom on treatments. This scale is simpler and easier in daily outpatient practice. As for the primary outcome of this study, we used both the cough scale as a subjective index and capsaicin cough threshold as an objective one.

The SCSS was not related to capsaicin cough threshold at the start of the itraconazole trial. In addition, the change in the SCSS after the treatment (itraconazole or placebo) was not related to the change in the capsaicin cough threshold. This was the case because some patients without cough hypersensitivity similar to CVA [11, 20] were included in the 21 patients.

When culturing sputum for detection of eumycetes, it should be noted that although it requires only approximately 2 days for detecting *Aspergillus*, approximately 10 days are required for culturing BM. During the 10th annual meeting of the Japan Cough Research Society, it was found that several laboratories store the nutrient medium only for approximately 2 days. This renders the detection of BM impossible in the institutions that discard the culture medium after 2 days.

It was remarkable that the low-dose itraconazole was efficacious after the trial phase in all 21 of the patients who did not have an existing diagnosis. As a result, the treatment with proton-pump inhibitors for suspected GER-associated cough was not required for anyone in this study after administration of itraconazole.

Thus, the 21 patients described here entailed the following manifestations: (1) chronic cough; (2) the presence of environmental fungi, particularly basidiomycetous (BM) fungi, in the sputum; and (3) good clinical response to antifungal drugs. These clinical features may constitute a unique disease concept termed fungus-associated chronic cough (FACC).

The participation in planning of the antifungal drugs in the cough treatment strategy is useful, and the clinical application has far-reaching possibilities. We hope that the recognition of FACC and the further investigation concerning appropriate uses of the anti-fungal drugs may provide an alternative useful avenue for the treatment of these otherwise difficult-to-manage patients. In addition, because the relationship between exposure to environmental fungi and the onset of the cough attacks has not been clearly understood, further studies [29] are also required in the future.

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