Factors Associated with Indacaterol Response in Tuberculosis-Destroyed Lung with Airflow Limitation

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Background: Pulmonary tuberculosis can result in anatomical sequelae, and cause airflow limitation. However, there are no treatment guidelines for patients with a tuberculosis-destroyed lung. Recently, indacaterol effectiveness in chronic obstructive pulmonary disease (COPD) patients with Tuberculosis history (INFINITY) study revealed indacaterol provided bronchodilation and symptom improvement in COPD patients with a tuberculosis-destroyed lung.

Methods: We conducted a *post-hoc* subgroup analysis of the randomized controlled trial, the INFINITY study, to determine factors associated with indacaterol response in a tuberculosis-destroyed lung with airflow limitation. Data from 68 patients treated with inhaled indacaterol, were extracted and analyzed. Factors associated with the response of forced expiratory volume in one second (FEV_1) to indacaterol treatment, were determined using linear regression analysis.

Results: Of 62 patients included, 68% were male, and 52% had history of cigarette smoking. Patients revealed mean FEV_1 of 50.5% of predicted value with mean improvement of 81.3 mL in FEV_1 after indacaterol treatment for 8 weeks. Linear regression analysis revealed factors associated with response of FEV_1 to indacaterol included a short duration of smoking history, and high short-acting bronchodilator response. When patients with history of smoking were excluded, factors associated with response of FEV_1 to indacaterol included high short-acting bronchodilator response, and poor health-related quality of life score as measured by St. George's Respiratory Questionnaire for COPD.

Conclusion: In a tuberculosis-destroyed lung with airflow limitation, short-acting bronchodilator response and smoking history can play a critical role in predicting outcomes of indacaterol treatment.

Keywords: Tuberculosis; Pulmonary Disease, Chronic Obstructive; Indacaterol; Smoking

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Introduction

Tuberculosis is the leading cause of death from a single infectious agent. In 2016, an estimated 10.4 million people fell ill with tuberculosis; and its global mortality was estimated at 1.3 million human immunodeficiency virus (HIV)-negative people and 0.37 million HIV-positive people[1]. Pulmonary tuberculosis can result in anatomical sequelae, and cause deterioration of lung functions[2-4]. A study has reported significant pulmonary impairments in more than half of patients treated for tuberculosis[5]. The patients with tuberculosis sequelae are thought to be a significant contributor to chronic obstructive pulmonary disease (COPD) population[6].

Unfortunately, there are no treatment guidelines for patients with tuberculosis-destroyed lung. In tuberculosis-endemic

areas, some patients with tuberculosis-destroyed lung may be diagnosed with and treated for COPD because of airflow limitations. A recent study suggests that follow-up care after the completion of tuberculosis treatment is important along with an overall improvement in treatment strategies[6]. A previous report suggested that the inhaled tiotropium may lead to improvement in patients with tuberculosis-destroyed lung[7]. The indacaterol effectiveness in COPD patients with Tuberculosis history (INFINITY) study showed that, relative to placebo, inhaled indacaterol 150 μg once-daily provided bronchodilation and symptom improvement in COPD patients with tuberculosis-destroyed lung[8]. However, the clinical factors related to the treatment response to indacaterol were not thoroughly explained in the study[8]. Thus, the study described here aims to determine the factors associated with the response to indacaterol treatment in tuberculosis-destroyed lung with airflow limitation.

Materials and Methods

1. Study design and patients

This *post-hoc* analysis used data collected in the previously reported INFINITY study[8]. The objective of this study was to determine the factors associated with response to indacaterol 150 μg once-daily in patients with tuberculosis-destroyed lung and moderate-to-severe airflow limitation. The treatment response was evaluated by the change from baseline in trough forced expiratory volume in 1 second (FEV_1) at week 8 of indacaterol treatment.

Briefly, the INFINITY study was a multicenter, randomized, double-blind, placebo-controlled, 8-week trial conducted in South Korea. Eligible patients were aged ≥19 years, had moderate-to-severe airflow limitation (post-bronchodilator FEV_1/forced vital capacity [FVC] <0.7, and post-bronchodilator FEV_1 ≥30% and <80% of predicted values), and a history of tuberculosis with no change in the chest radiologic test over the past 1 year, regardless of smoking history. All patients had at least one finding of destroyed parenchyma, including lung volume loss, bronchovascular distortion, fibrosis, and bronchiectasis. Exclusion criteria included a history of asthma, respiratory infection or COPD worsening within the previous 6 weeks. After screening, eligible patients were randomized to either a placebo or treatment groups. The treatment group (n=68) received once-daily indacaterol 150 μg through the Breezhaler device (Novartis Pharma AG, Stein, Switzerland) for 8 weeks.

Because this study is a *post-hoc* analysis using the data from the previous clinical trial, written informed consent was waived. The study protocol was approved by the Institutional Review Board of Asan Medical Center (2018-0509).

2. Statistical analysis

We compared characteristics of study subgroups using the unpaired t-test for continuous variables and Fisher exact test for categorical variables. We tested the correlation between the response of FEV_1 to indacaterol treatment and the subtypes of leukocytes or parameters of lung functions, using the Pearson's correlation coefficient.

To determine the factors associated with the response of FEV_1 to indacaterol treatment, we performed linear regression analysis. Variables identified as significant in univariate analysis were additionally evaluated for the risk-adjusted relationship with the response of FEV_1. The multivariate analysis was processed for seven factors, including age, sex, body mass index (BMI), smoking history (pack-years), spirometry finding (FEV_1, % of predicted value), short-acting bronchodilator response, and St. George's Respiratory Questionnaire for COPD (SQRQ-C), using the enter and stepwise backward elimination method.

Statistical analyses were performed using the SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Data are expressed as number (%) or mean±standard deviation, and a p-value of <0.05 was considered statistically significant.

Results

1. Characteristics of patients

We analyzed 62 patients, who completed the study, among the 68 patients in the indacaterol treatment group. Therefore, baseline characteristics were similar to data of the original report[8]. Table 1 summarizes the baseline characteristics of the study population. The mean age of patients was 64.6 years, 67.7% were males, and the overall mean BMI was 21.6 kg/m². Overall, 32 patients (51.6%) had a smoking history with a mean of 34.9 pack-years. There were only four reports of exacerbations within the previous year (6.5%). Radiologically, lung volume loss (88.7%) was the most common finding, followed by fibrosis (66.1%), bronchovascular distortion (51.6%), and bronchiectasis (50%).

Characteristics of lung function were as follows: mean FVC, 2.58 L (72.3% predicted) and FEV_1, 1.32 L (50.5% predicted). The reversibility of FEV_1 by short-acting bronchodilator was 103.2 mL (mean). After inhaled indacaterol treatment for 8 weeks, the improvement of FEV_1 was calculated to be 81.3 mL (mean). The overall mean baseline dyspnea index focal score was calculated to be 7.3; COPD assessment test score, 15.4; and SGRQ-C score, 37.9.

2. Factors related with the response to indacaterol

Table 2 shows the clinical factors associated with the re-

Table 1. Baseline demographic and clinical characteristics

	Value
Age, yr	64.6±10.8
Male sex	42 (67.7)
BMI, kg/m^2	21.6±3.4
Ever smokers	32 (51.6)
Smoking duration, pack-years	34.9±27.2
COPD exacerbation in previous years	4 (6.5)
Radiologic findings	
Lung volume loss	55 (88.7)
Bronchovascular distortion	32 (51.6)
Fibrosis	41 (66.1)
Bronchiectasis	31 (50.0)
Pulmonary functions	
FVC, L	2.58±0.73
FVC, % of predicted value	72.3±13.2
FEV$_1$, L	1.32±0.39
FEV$_1$, % of predicted value	50.5±11.9
Bronchodilator response (FEV$_1$), mL	103.2±96.0
FEV$_1$/FVC, %	52.1±9.9
Symptom scores	
BDI focal score	7.3±2.1
CAT score	15.4±7.6
SGRQ-C total score	37.9±18.7

Values are presented mean±standard deviation or number (%).
BMI: body mass index; COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 second; Bronchodilator response: bronchodilator response by short-acting bronchodilator; BDI: baseline dyspnea index; CAT: COPD assessment test; SGRQ-C: St. George's Respiratory Questionnaire for COPD.

sponse of FEV$_1$ to indacaterol treatment. In a univariate analysis, the response amount of FEV$_1$ to indacaterol treatment was associated with smoking history (p=0.021) and short-acting bronchodilator response (p<0.001). The response of FEV$_1$ by indacaterol treatment demonstrated statistically significant positive correlation with the amount of short-acting bronchodilator response in FEV$_1$ (ρ=0.385, p=0.002; r=0.443, p<0.001) (Figure 1) and smoking history in pack-years (r=−0.292, p=0.021) (Figure 1). However, age, sex, BMI, FEV$_1$, and SGRQ-C score did not affect the response of FEV$_1$ to treatment with indacaterol in linear regression analysis. Risk-adjusted analysis revealed that indacaterol response was mostly associated with a short smoking history (p=0.018), and high short-acting bronchodilator response (p=0.004). Based on the multivariate analyses using the stepwise backward elimination method, this study also demonstrated that indacaterol response was independently associated with two factors: smoking history (p=0.016), and baseline short-acting bronchodilator response (p<0.001).

3. Factors related with the response to indacaterol: subgroup analysis according to cigarette smoking

Table 3 presents a comparison of smokers and nonsmokers, in terms of clinical factors associated with response to indacaterol treatment. In smokers, short smoking history (p=0.019) and high short-acting bronchodilator response (p=0.045) were associated with indacaterol response. However, in nonsmokers, a worse score in health-related quality of life by SGRQ-C (p<0.001), and higher short-acting bronchodilator response (p=0.001) were related to the response to indacaterol. While 96.9% of smokers were males, only 36.7% of nonsmokers were males. Thus, we analyzed 42 males in total. Both groups had similar clinical and radiologic features. However, the smokers had a mean smoking history of 35.4 pack-years, and lower SGRQ-C score (38.8±16.1 vs. 23.5±14.8,

Table 2. Factors associated with the response of FEV$_1$ to indacaterol treatment

	Univariate			Multivariate		
	Beta	Standard error	p-value	Beta	Standard error	p-value
Age	−1.524	1.920	0.431	0.019	1.847	0.992
Male sex	42.381	43.969	0.339	−8.367	48.728	0.864
BMI, kg/m^2	6.579	6.136	0.288	3.389	5.573	0.546
Smoking history, pack-year	−1.804	0.764	0.021*	−2.169	0.888	0.018*
FEV$_1$, % pred.	−2.017	1.736	0.250	1.487	1.788	0.409
BDR (FEV$_1$), mL	0.747	0.195	<0.001***	0.654	0.219	0.004**
SGRQ-C	2.052	1.087	0.064	1.684	1.202	0.167

*p<0.05, **p<0.01, ***p<0.001.
FEV$_1$: forced expiratory volume in 1 second; BMI: body mass index; BDR: short-acting bronchodilator response; SGRQ-C: St. George's Respiratory Questionnaire for chronic obstructive pulmonary disease.
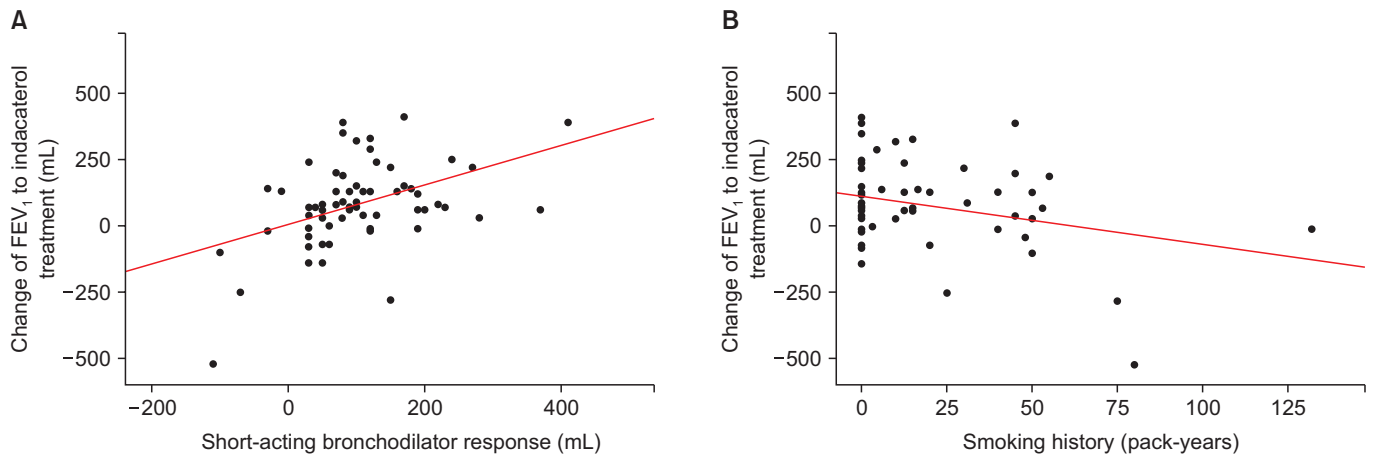
Figure 1. Correlation between short-acting bronchodilator response (A) or smoking history (B) and the response of forced expiratory volume in 1 second (FEV$_1$) to indacaterol treatment.

Table 3. Factors associated with the response of FEV$_1$ to indacaterol treatment according to smokers and non-smokers

	Smokers (n=32)			Nonsmokers (n=30)		
	Beta	Standard error	p-value	Beta	Standard error	p-value
Age	−4.325	2.901	0.146	1.917	2.412	0.434
Male sex	60.645	189.513	0.751	46.220	51.977	0.381
BMI, kg/m²	5.496	10.722	0.612	7.141	6.915	0.311
Smoking history, pack-year	−2.801	1.125	0.019*			
FEV$_1$, % pred.	−3.168	2.425	0.201	0.697	2.681	0.797
BDR (FEV$_1$), mL	0.621	0.297	0.045*	0.940	0.241	0.001**
SGRQ-C	−0.837	2.050	0.686	3.901	0.974	<0.001***

*p<0.05, **p<0.01, ***p<0.001.
FEV$_1$: forced expiratory volume in 1 second; BMI: body mass index; BDR: short-acting bronchodilator response; SGRQ-C: St. George's Respiratory Questionnaire for chronic obstructive pulmonary disease.

p=0.010). Of the radiologic findings, fibrosis was more common in smokers than nonsmokers (80.6% vs. 36.4%, p=0.019).

4. Relation of radiologic findings with the response to indacaterol

Supplementary Table S1 summarizes the response of FEV$_1$ to indacaterol treatment based on the radiologic findings. Clinically significant abnormal findings were observed in 52 patients (83.9%). There was no significant difference in the response of FEV$_1$ to indacaterol treatment between patients with abnormal findings (15.0±251.4 mL) and those without abnormal findings (94.0±138.2 mL, p=0.159). In patients with lung volume loss, the response of FEV$_1$ to indacaterol treatment was 77.3±153.4 mL; however, there was no difference in patients without lung volume loss (112.9±229.7 mL, p=0.703). Patients with fibrosis showed a 66.3±122.6 mL change in FEV$_1$; however, patients without fibrosis had a 110.5±220.0 mL change in FEV$_1$ (p=0.313). There was no significant difference between patients with bronchovascular distortion (100.6±154.9 mL) and those without bronchovascular distortion (60.7±168.9 mL, p=0.337). The response of FEV$_1$ to indacaterol treatment was 66.1±154.8 mL in patients with bronchiectasis, and this response was similar to patients without bronchiectasis (96.5±170.0 mL, p=0.465). Overall, 15 patients (24.2%) showed all four abnormal radiologic findings with a 42.7±113.6 mL change in FEV$_1$.

Discussion

This *post-hoc* analysis of the INFINITY study aimed to identify the characteristics of responders to indacaterol 150 µg once-daily in patients with tuberculosis-destroyed lung with moderate-to-severe airflow limitation. In the current study, the response of FEV$_1$ to indacaterol treatment demonstrated

significant positive correlation with short-acting bronchodilator response. Patients with better response to indacaterol treatment exhibited a clinical phenotype with high short-acting bronchodilator response and short duration of tobacco smoking. These data suggest that short-acting bronchodilator response and smoking history can be important factors in predicting the response to indacaterol treatment in patients with tuberculosis-destroyed lung with airflow limitation. Additionally, there were differences in clinical factors between smokers and nonsmokers related to response to indacaterol treatment. In nonsmokers, indacaterol response was associated with short-acting bronchodilator response and SGRQ-C.

Pulmonary tuberculosis can result in airflow obstructions, particularly in those with a long-standing history of the disease, and if the extent of parenchyma involvement is extensive[9]. However, there are no treatment guidelines for patients with tuberculosis-destroyed lung. Recently, the INFINITY study provided some evidence for management of tuberculosis-destroyed lung with airflow limitation. In the currrent study, we determined the factors related to the response to indacaterol treatment in tuberculosis-destroyed lung with airflow limitation. FEV_1 reversibility by short-acting bronchodilator was an independent factor associated with the response of FEV_1 to indacaterol treatment. In COPD, a short-acting bronchodilator reversibility test has been employed to identify patients with different disease course and has also been used to predict long-term response to bronchodilators[10]. However, most studies suggest that the reversibility to short-acting bronchodilator does not predict long-term response to bronchodilator maintenance therapy because of various confounding effects[11-14]. Nonetheless, the role of reversibility caused by short-acting bronchodilator use was not completely investigated in tuberculosis-destroyed lung with airflow limitation. It has been shown that reversibility in patients with tuberculosis-destroyed lung was significantly poor compared to those with COPD[15]. This result explained by attributing airflow obstruction in tuberculosis-destroyed lung more to mechanical destruction and stenosis rather than contraction of the smooth muscles of the airway[15]. However, there is still unclear in the clinical role and the mechanism of reversibility in tuberculosis-destroyed lung.

In the current study, heavy-smoking history was another independent factor related to poor response to indacaterol treatment. Tobacco smoking is a major cause of the development of COPD and the risk increases in a dose-dependent manner with the increase in pack-years[16]. The relationship between smoking and the rate of lung function decline has been well established in the general population[17]. However, there is still controversy surrounding the difference in lung function between nonsmoker and smoker COPD patients[18-22]. Furthermore, the role of smoking in patients with tuberculosis-destroyed lung has not been established. Some papers have demonstrated that tuberculosis in smokers results in

a severe disseminated clinical course and extensive lung involvement[9,23]. Our study showed that nonsmokers have different clinical features associated with indacaterol response compared with smokers. It has been previously suggested that the sex ratio of each study may impact the study results, as a selection bias, in clinical differences between nonsmoker and smoker COPD patients[24]. Furthermore, our study had a significant difference in sex ratio between smokers and nonsmokers. However, the analysis of male patients showed that smokers had exacerbated symptoms and a higher degree of fibrosis. A previous COPD study have also shown that COPD patients who were smokers had more chronic cough, and sputum than nonsmoker COPD patients[24]. Some studies have demonstrated that smoker COPD patients have a greater incidence of emphysema than nonsmoker COPD patients[18,22,24,25]. However, we could not determine the role of smoking in emphysema. Further investigations are required to evaluate the role of smoking in patients with tuberculosis-destroyed lung with airflow limitation.

Bronchial and parenchymal destruction by tuberculosis induce radiologic changes, including lung volume loss, bronchiectasis, bronchovascular distortion, and fibrotic bands[26]. In the current study, we analyzed the relationship between these four common radiologic findings and their response to indacaterol treatment in tuberculosis-destroyed lung with airflow limitation. Although not statistically significant, reduced treatment responses were observed in patients with lung volume loss, fibrosis, and bronchiectasis. Strangely, there was a trend toward improved treatment response with bronchovascular distortion. This difference might be attributed to differences affecting structure and function of the lung, associated vascular complications, and parenchymal or airway lesions. In tuberculosis-destroyed lung, additional studies are still required to determine the ability of various radiologic findings to predict lung functions and treatment responses. A recent study on tuberculosis-destroyed lung showed no differences in the incidence of pleural thickening or bronchiectasis between patients with and without airflow obstruction[15]. Also, pleural thickening did not affect the decline in lung function. However, Jung et al.[3] reported that inactive tuberculosis lesion, in the upper lobe with dominant, discrete linear or reticular opacities, with or without calcification, on chest X-ray was an important risk factor for determining airflow obstruction.

This study has several limitations. First, it included a small sample size, because it was a *post-hoc* subgroup analysis used only one arm of the INFINITY study. However, the INFINITY study was conducted as a multicenter, randomized, double-blind, placebo-controlled study. Thus, the results of this investigation are novel, despite the small sample size. However, a more extensive study is required to predict the response to indacaterol treatment in tuberculosis-destroyed lung with airflow limitation. A second potential limitation could be that not all confounding factors were analyzed, such as biomass

fuel exposure or socioeconomic status. These factors could affect the progression of airflow obstruction or sequelae of tuberculosis. Third, this study did not reflect the characteristics of tuberculosis-destroyed lung without airflow limitation. As previously mentioned, treatment guidelines for patients with tuberculosis-destroyed lung have not been established. Hence, further investigations are warranted to determine the pharmacological agents and to predict the treatment response for patients with tuberculosis-destroyed lung, regardless of airflow obstruction.

In tuberculosis-destroyed lung with airflow limitation, short-acting bronchodilator response correlates with FEV_1 response to inhaled indacaterol treatment. In addition, the improvement of lung function is independently related to short smoking history as well as high short-acting bronchodilator response. In nonsmokers, high short-acting bronchodilator response, and poor health-related quality of life score as measured by SGRQ-C were related to indacaterol response in tuberculosis-destroyed lung with airflow limitation.

Authors' Contributions

Conceptualization: Oh YM. Methodology: Oh YM, Kim TH. Formal analysis: Oh YM, Kim TH, Rhee CK. Writing - original draft preparation: Kim TH. Writing - review and editing: Oh YM, Rhee CK. Approval of final manuscript: all authors.

Conflicts of Interest

The authors declare no competing financial interests. The INFINITY study data was generously provided by Novartis, but no financial, statistical, or personal support was provided for this study.

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Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

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Supplementary Table S1. Responses of FEV$_1$ to indacaterol treatment, according to radiologic findings

Radiologic finding		No. (%)	δFEV$_1$ (mL)	p-value
Without	Lung volume loss	7 (11.3)	112.9±229.7	0.703
With	Lung volume loss	55 (88.7)	77.3±153.4	
Without	Bronchovascular distortion	30 (48.4)	60.7±168.9	0.337
With	Bronchovascular distortion	32 (51.6)	100.6±154.9	
Without	Fibrosis	21 (33.9)	110.5±220.0	0.313
With	Fibrosis	41 (66.1)	66.3±122.6	
Without	Bronchiectasis	31 (50.0)	96.5±170.0	0.465
With	Bronchiectasis	31 (50.0)	66.1±154.8	

Values are presented as numbers (%) and mean±standard deviation.
FEV$_1$: forced expiratory volume in 1 second; δFEV$_1$: change from baseline in trough FEV$_1$ after 8 weeks.