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Itraconazole Improved Bronchial Wall Thickness in Severe Persistent Asthma: A Double-blind Placebo-controlled Randomized Clinical Trial

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ABSTRACT

The purpose of this study was to evaluate the effect of 8 months of treatment with itraconazole on airway wall thickness in patients with severe persistent asthma.

It was a double-blind, randomized, placebo-controlled clinical trial (IRCT20091111002695N9). Seventy-five subjects with severe persistent asthma received itraconazole (100 mg), prednisolone (5 mg), or placebo twice a day for eight months in three treatment groups (n=25 in each group). The primary objective was to improve the right upper lobe apical segmental bronchus (RB1) wall thickness percentage measured by high-resolution computed tomography scan of the lungs. Other morphometric measurements of RB1, asthma control test (ACT) score, presence of wheezing, dyspnea severity, rate of asthma exacerbation, fractional exhaled nitric oxide (FeNO), and expiratory volume in 1 second (FEV1) were set as the secondary outcomes.

Wall thickness percentage reduced significantly from 46% to 43.7% from pre- to post-treatment in the itraconazole-treated subjects. Similarly, lumen area and radius increased significantly in both the prednisolone and itraconazole groups. Itraconazole led to a significant improvement in wheezing, dyspnea severity, FEV1, ACT score, and FeNO. Although prednisolone was also effective in improving pulmonary function tests and ACT scores, it was associated with significantly more side effects than itraconazole.

Long-term treatment with itraconazole resulted in a significant reduction in bronchial wall thickness and improvements in clinical findings and pulmonary function tests. Thus, itraconazole could be a helpful add-on treatment option for severe persistent asthma patients to achieve better disease control.

Keywords: Airway remodeling; Asthma; Itraconazole; X-ray computed tomography

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INTRODUCTION

It is estimated that severe persistent asthma (SPA) represents 5% to 10% of the total asthma population,

which is regarded as a significant health burden.[1] SPA cannot be controlled in spite of using the maximum dose of optimized therapy and treatment of its contributory factors; or it will worsen if the maximum dose treatment is decreased.[2] Significant efforts have been made to develop new therapies and treatment strategies to control this type of asthma. Long-term use of corticosteroids in these subjects may be associated with various complications, such as infections, diabetes, osteoporosis, and psychiatric disorders. Even a low dose of inhaled corticosteroids (ICS) is not free of complications.[3,4]

Exposure to foreign aerobiological particles such as fungi can lead to adverse effects, including respiratory infections, irritation, and inflammation in patients with asthma.[5,6] In addition, using ICS over an extended period of time in patients with SPA provides a permissive environment for fungi to colonize the airways.[7] Studies on allergic bronchopulmonary aspergillosis (ABPA) showed that fungal colonization initiates an inflammatory and immunological response that may not respond appropriately to ICS treatment and can stimulate SPA. Different inflammatory mediators such as interleukin (IL)-4, IL-5, IL-13, IL-17, transforming growth factor beta (TGF-β), and vascular endothelial growth factor receptor 2 (VEGFR2), which are released from inflammatory cells, promote the release of growth factors and induce airway remodeling.[8,9] This phenomenon is characterized by airway structural changes such as smooth muscle hypertrophy, subepithelial fibrosis, neovascularization, and wall thickness.[10] In addition, it has been shown that increased wall thickness and airway narrowing during remodeling are associated with severe asthma symptoms and decreased pulmonary function.[11-13] Remodeling could be assessed by measuring bronchial wall thickness in a high-resolution computed tomography (HRCT) scan of the lungs.

On the other hand, it has been shown that antifungal treatments, including itraconazole, have a positive influence on asthmatic patients, especially those with SPA.[14-16] This effect is probably due to the reduction of airways fungi burden that may finally lead to modification of inflammatory response and change of airway wall structure. No publication about the effect of itraconazole on airway remodeling is available. So, we designed this randomized, double-blind, placebo-controlled clinical trial to investigate the effect of itraconazole on airway remodeling and bronchial structure in SPA patients by measuring the dimensions of the right upper lobe apical segmental bronchus (RB1) bronchus in HRCT. The results might help us to broaden our knowledge about asthma remodeling and the effect of antifungal therapy on asthma remodeling and its optimum management.

PATIENTS AND METHODS

Trial Design

In this randomized, double-blind, placebo-controlled, phase 2 clinical trial, we investigated the effect of 8 months of treatment with itraconazole on airway wall thickness as an indicator of airway remodeling in patients with SPA (Figure 1). This study was conducted between May 2019 and April 2021 at a tertiary clinic of pulmonary diseases located in Mashhad, Iran. This clinical trial has been approved by the Iranian Registry of Clinical Trials (IRCT20091111002695N9) and the National Committee for Ethics in Biomedical Research (IR.IAU.MSHD.REC.1398.030). Written informed consent was obtained from all subjects prior to enrollment.

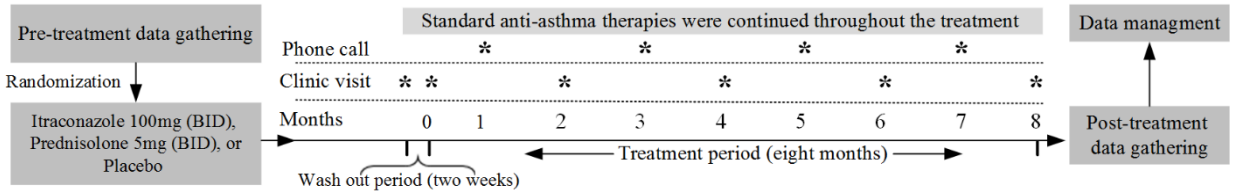


Figure 1. Study design
Standard asthma medications were continued throughout the study.

Study Population and Treatment Groups

The inclusion criteria included (a) ages 18 to 65 years; (b) being diagnosed with asthma based on the Global Initiative for Asthma (GINA) definition;[17] (c) suffering from SPA defined as requiring high dose ICS in addition to another controller (eg, leukotriene modifier, long-acting β2 agonist, theophylline) or a systemic corticosteroid to keep asthma controlled or which remains symptomatic in spite of adherence to this therapy.[2] Subjects were excluded in cases of (a) drug allergy to itraconazole; (b) ABPA; (c) breastfeeding; (d) pregnancy; (e) current or former smokers; or (f) gastroesophageal disorder. Participants were withdrawn in the case of (a) loss to follow-up; (b) informed consent withdrawal; (c) an adverse event with a high risk to the participant's health; (d) becoming pregnant during the study; or (e) confirmed elevated hepatic enzymes.

Medications, Randomization, and Blinding

Itraconazole and prednisolone raw materials were provided by Tehran Darou Company, Iran. Capsules were filled with the medications by means of fully automatic equipment (formulated, mixed, and filled) in partnership with the pharmacology section of Mashhad University of Medical Sciences. Placebo capsules were filled with lactose.

A randomization list was created (www.sealedenvelope.com) and subsequently balanced between the 3 treatment groups: (a) itraconazole (100 mg, bid) as the test drug (dosage was determined based on the previous studies),[18-20] (b) prednisolone (5 mg, bid) as the active control therapy as it is currently the standard treatment for SPA, and (c) placebo (lactose, bid).

All the medications were prepared with identical soft gelatin capsules and drug containers. The only difference was the random codes on the labels of the drug containers. Patients received one of the drug containers randomly at the beginning and continued receiving the allocated medication according to that specific code on the subsequent visits.

Intervention and Outcomes

Baseline demographic data and clinical findings such as wheezing, dyspnea severity, annual asthma exacerbations rate, and asthma control test (ACT) score were recorded. Complete blood cell count, serum levels of total immunoglobulin E, lung HRCT scan (to screen for ABPA), and pulmonary function tests were performed. Then, each participant was randomly given one of the medications and a follow-up card containing a table to record the asthma exacerbations. After a two-week washout period, patients received the allocated treatment for 8 months. In addition to investigational drugs, patients continued their standard anti-asthma therapies throughout the treatment period. Regular telephone-based follow-up and clinic visits were scheduled to observe the patients closely. Adverse events were immediately reported to the principal investigator to assess their relation to the study drug. After 8 months of treatment, subjects were assessed again, and pulmonary function tests and HRCT scans were repeated.

The primary outcome of this study was the change in wall thickness percentage (WT%) of the right upper lobe apical segmental bronchus (RB1). The secondary outcomes of this trial were morphometric measurements of the RB1 bronchus other than WT%, improvement in clinical findings (including wheezing and dyspnea severity), annual asthma exacerbations rate, ACT score, forced expiratory volume in 1 second (FEV1), and fractional exhaled nitric oxide (FeNO).

Measuring Airway Dimensions

A conventional 16-slice configuration CT scanner (Siemens) with a 24-row adaptive detector array (gantry rotation time 0.5 second, pitch 0.83, collimation 0.5 mm, 200 mA, 120 kV) was used to perform the morphometric measurement of the bronchial wall. Sixteen slices per rotation were acquired, but later 32 slices were reconstructed with high spatial resolution using a standard reconstruction algorithm (reconstruction section thickness of 1 mm, intervals of 0.5 mm). The HRCT scans were done in the supine position at full inspiration, and participants were asked to administer long-acting β_2-agonists 2 hours prior to the scan.

RB1 bronchus dimensions were measured randomly by 2 experienced radiologists blinded to the treatment and dates of scans. The average values were divided by body surface area ($BSA=\sqrt[2]{\frac{\text{height (cm)}\times\text{weight(kg)}}{3600}}$) to reduce the effects of weight and height on bronchus dimensions. Our radiologists used 3D Slicer software (http://www.slicer.org, Surgical Planning Laboratory, Harvard University, Boston, MA, USA, version 4.10.2) to detect and measure the airway cross-sectional

dimensions, including mean outer radius (OR/BSA), mean inner radius (IR/BSA), wall thickness/BSA (WT/BSA), lumen area (LA/BSA), and wall area/BSA (WA/BSA) (Figure 2).[21] Later, we calculated the WT percentage ($WT\% = \frac{WT}{OR} \times 100$) and WA percentage ($WA\% = \frac{WA}{\text{Total area}} \times 100$) based on these measurements.

Statistical Analysis

The estimated sample size was 75 subjects, who were divided into 3 groups. All data analyses are considered explorative due to the absence of a statistical power calculation because of the pilot nature of this clinical trial. Parametric data were compared by ANOVA or paired *t* test. Kruskal–Wallis, Mann–Whitney U, and Mcnemar tests were used to compare nonparametric data. GraphPad Prism software version 8.0.2 (GraphPad Software, San Diego, California, USA) and IBM SPSS Statistics (IBM Corporation, version 19.0) were used to perform data analysis. *p* values below 0.05 were considered statistically significant.

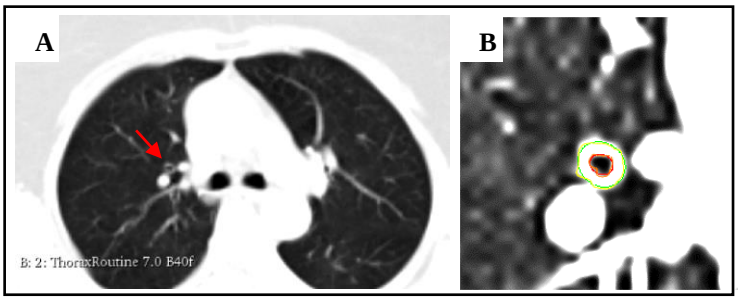


Figure 2. Right upper lobe apical segmental bronchus (RB1) dimensions. (A) RB1 is shown by a red arrow. (B) The outer (green) and inner (red) borders of RB1 were detected by the software.

RESULTS

A total of 88 patients with SPA were treated with itraconazole, prednisolone, or placebo in addition to standard asthma controllers during the trial (Figure 3). Thirteen participants did not finish the treatment period due to either withdrawal of informed consent or experiencing adverse events. Two participants were lost to follow-up, and 75 were included in the data analysis. Baseline characteristics were well-balanced among the treatment groups (Table 1).

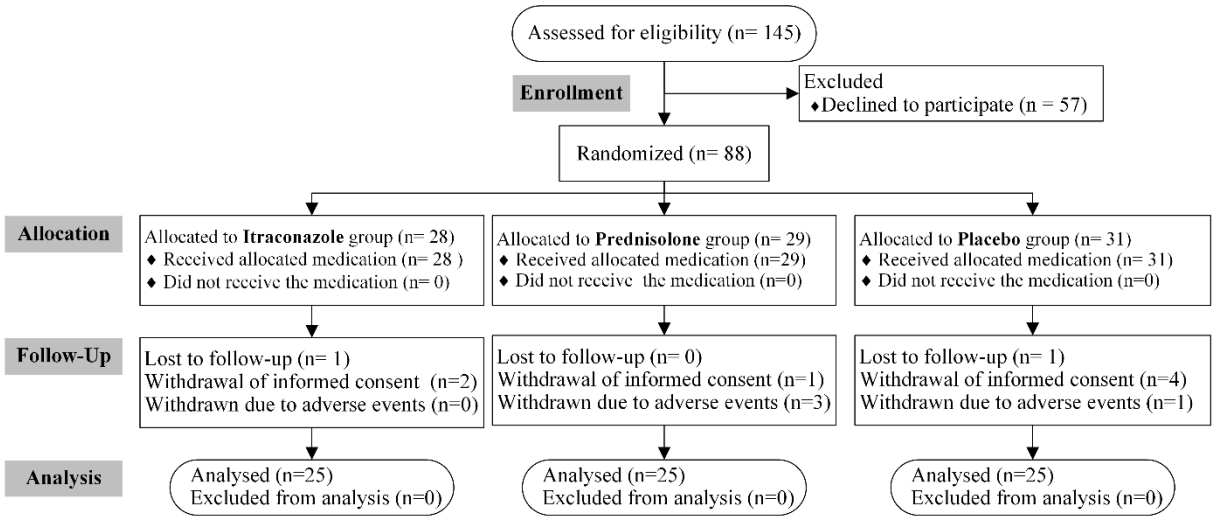


Figure 3. CONSORT flow diagram for severe persistent asthma participants in Itraconazole, Prednisolone, or Placebo groups.

Table 1. Demographic and clinical baseline characteristics of subjects suffering from severe persistent asthma

Characteristic		Itraconazole (n=25)	Prednisolone (n=25)	Placebo (n=25)	*p*
Females		18 (72%)	21 (84%)	20 (80%)	0.57
Age (years)		53.5 ± 9.6	56.5 ± 11.2	54.4 ± 8.9	0.54
Duration of asthma (years)		10 [8-12]	9 [6.5-12.5]	9 [6-11]	0.076
Body surface area (m^2)		1.76 ± 0.19	1.72 ± 0.18	1.81 ± 0.17	0.54
ACT score		11.3 ± 2.5	11.5 ± 2	10.9 ± 2.9	0.57
Dyspnea severity †	Moderate	5 (20%)	3 (12%)	4 (16%)	0.74
	Severe	12 (48%)	14 (56%)	16 (64%)	
	Extremely severe	8 (32%)	8 (32%)	5 (20%)	
Presence of wheeze		23 (92%)	24(96%)	23 (92%)	0.8
Spirometry	FEV1 (L)	1.89 ± 0.48	60.3 ± 14.6	1.12 ± 0.33	0.85
	FEV1/FVC (%)	1.93 ± 0.77	62.7 ± 15	1.18 ± 0.41	0.68
	FEF_{25-75} (L)	1.83 ± 0.58	58.8 ± 17.5	1.06 ± 0.32	0.51
FeNO (ppb)		31 [30 -70]	35 [18.5-80]	37 [28.5-58.5]	0.41
Total serum IgE (IU/ml)		136.5 [98-187]	119.3 [60.3-164]	143 [99-228]	0.68
Eosinophil count in blood $\times 10^9$/L		0.25[0.11-0.27]	0.25[0.15-0.37]	0.2 [0.13-0.25]	0.5
Neutrophil count in blood $\times 10^9$/L		5.38 ± 1.9	4.72 ± 2.5	5.94 ± 2	0.21

Data are presented as mean ± standard deviation, median [interquartile range], or number (percentage). ACT, Asthma Control Test; FEF_{25-75}, forced expiratory flow at 25–75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ppb, parts per billion; IgE, immunoglobulin E.
† Moderate indicates having more than two days (but less than 7 days) of dyspnea per week, severe indicates experiencing dyspnea all days of the week, and extremely severe indicates having persistent dyspnea.

HRCT Measurements

RB1 bronchus dimensions are summarized in Table 2. In the itraconazole-treated subjects, WT% changed from 46% to 43.7% from pre- to post-treatment, which was statistically significant (p<0.01). Additionally, WT/BSA, WA/BSA, and WA% were significantly reduced at the end of the treatment compared to the initial values (all p<0.05). Interestingly, there was a significant increase in IR/BSA and LA/BSA in this group, a finding that was observed in prednisolone-treated subjects (both p<0.05). However, there was no statistically significant change in WT%, WT/BSA, WA%, or WA/BSA in the prednisolone group. Subjects who received the placebo had no significant change in RB dimensions.

Asthma Control

Data analysis showed that 13 subjects in the itraconazole group had improvement in dyspnea severity, which was significantly more than both the prednisolone (n=9, p<0.01) and placebo groups (n=2, p<0.01) (Figure 4). The number of prednisolone-treated subjects with improved severity of dyspnea (n=9) was significantly greater than that of placebo-treated subjects (n=2, p<0.05). Also, 23 itraconazole-treated subjects had wheeze on auscultation that reduced to 10 after the treatment period (p<0.001); therefore, 13 subjects became normal after the treatment period. This alteration was not significant in the other 2 groups, and the presence of wheeze changed from 24 to 18 (p<0.01) and 23 to 21 (p>0.999) in the prednisolone and placebo groups, respectively.

Further data analysis revealed that the median duration of time to first asthma exacerbation in itraconazole, prednisolone, and placebo-treated subjects were 290, 257, and 200 days, respectively. However, survival analysis showed no statistically significant difference in time to first asthma exacerbation among the treatment groups (all $p_{\text{Log-rank}}$>0.05) (Figure 5).

Table 2. Comparison of bronchial dimensions in severe persistent asthma treated in the three study groups

		IR/BSA (mm/mm)	WT/BSA (mm/mm)	WT% (%)	LA/BSA (mm^2/m^2)	WA/BSA (mm^2/m^2)	WA % (%)
Itraconazole	Baseline	1.25 ± 0.17	1.06±0.13	46 ±2.8	5.01 ±1.47	12.05 ±2.9	70.8 ±3.1
	Post-treatment	1.27 ± 0.18	0.99±0.16	43.7±4.8	5.24 ±1.52	11.18 ±3	68.1 ±5.5
	Mean difference	–0.02	0.07	2.29	–0.23	0.86	2.6
	p value	0.024	0.013	0.006	0.038	0.023	0.005
Prednisolone	Baseline	1.18 ±0.22	1.01±0.13	46.5±4.7	4.33 ±1.3	11.3 ±3.1	70.2 ±4.7
	Post-treatment	1.23 ±0.24	0.98±0.14	44.3±4.4	4.94 ±1.7	10.7 ±2.7	68.5 ±9.26
	Mean difference	–0.02	0.31	2.1	–0.6	0.32	2.4
	p value	<0.001	0.3	0.104	0.024	0.63	0.095
Placebo	Baseline	1.27±0.21	1.03±0.15	44.73±3.2	5.26 ±1.93	11.7 ±3.3	69.3 ±3.7
	Post-treatment	1.28±0.23	1.02±0.17	44.4 ±4.8	5.34 ±2.1	11.6 ±3.5	68.87 ±5.7
	Mean difference	0.05	0.008	0.32	–0.09	0.08	0.47
	p value	0.5	0.68	0.61	0.41	0.75	0.53

Values are presented as mean±standard deviation.
BSA, body surface area; IR, inner radius; LA, lumen area; mm, millimeter; WA, wall area; WT, wall thickness.

Further data analysis revealed that the ACT score increased significantly from 11.3 (2.5) to 16.5 (3.1) in the itraconazole group (p<0.001), from 11.5 (2) to 14 (3.4) in the prednisolone group (p<0.01), and from 10.9 (2.9) to 11.6 (2.7) in subjects who received the placebo (p<0.05). Also, itraconazole-treated subjects had significantly higher ACT scores than subjects who received prednisolone (p<0.05). However, the post-treatment ACT scores of both the itraconazole and prednisolone groups were significantly higher than the placebo group (both p<0.001).

FeNO and Spirometry

Median FeNO reduced significantly from 31 [IQR: 30-70] to 23 [IQR: 12.5-72] (p<0.05) and from 35 [IQR: 18.5-80] to 27 [IQR: 6-72.5] (p<0.01) in the itraconazole and prednisolone groups, respectively. In patients who received the placebo, it changed from 37 [IQR: 27.5-58.5] to 39 [IQR: 31-57.5], which was not statistically significant (p>0.999). Additionally, Pearson's correlation test suggested a weak negative correlation between the change in FeNO and baseline blood eosinophil count (r=0.335, p<0.05) in the prednisolone group (Figure 6). No correlation was found in other treatment groups.

Comparing before and after treatment pulmonary function tests (Table 3) revealed that subjects who received itraconazole had significant improvement in FEF_{25-75}, FEV1, and FEV1/FVC (all p<0.001). Prednisolone also improved the spirometry items significantly (all p<0.01). However, no significant change was observed in placebo-treated patients.

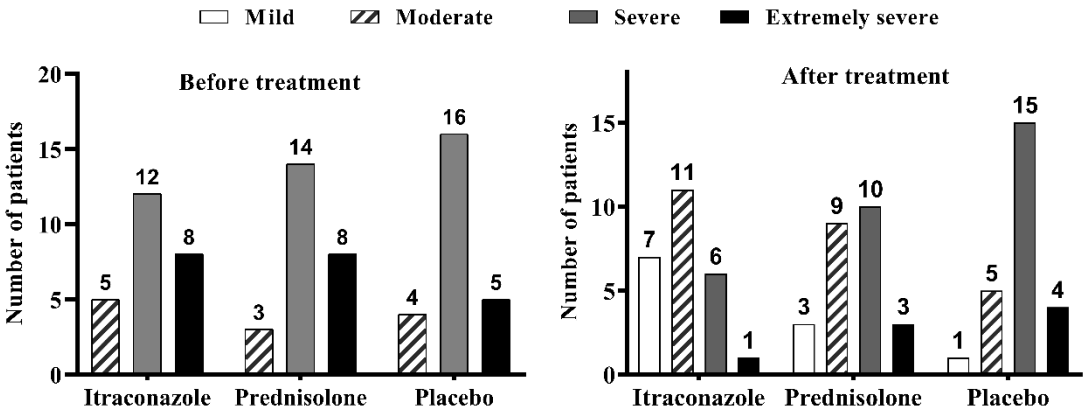
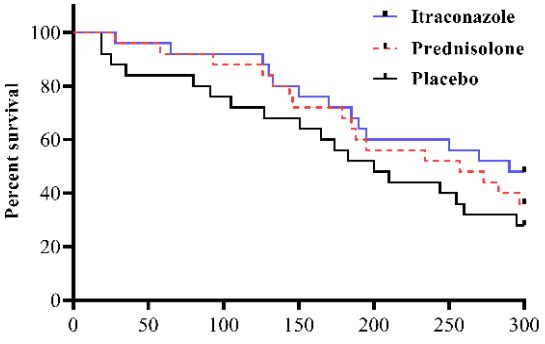


Figure 4. Bar graphs show dyspnea severity before and after the treatment. Mild (≤ 2 days a week), moderate (≥ 2 days per week and <every day), severe (every day), extremely severe (persistent).



No. at risk							
Itraconazole	25	25	23	19	15	14	9
Prednisolone	25	25	24	20	16	15	12
Placebo	25	22	19	18	13	11	7

	Itraconazole vs Placebo	Prednisone vs Placebo	Itraconazole vs Prednisolone
Hazard ratio	0.57	0.74	0.75
%95 CI	0.28-1.17	0.37- 1.45	0.36-1.57
$P_{\text{Log-rank}}$	0.12	0 .38	0.45

Figure 5. Kaplan-Meier curves demonstrating the number of subjects with no asthma exacerbation during the treatment

Adverse Events

One (3.5%) patient in the itraconazole group had nausea. Five prednisolone-treated subjects reported adverse events that led to withdrawal in 3 of them. Adverse events in this group included weight gain (n=3, 10.3%), headache (n=1, 3.4%), hair fall (n=1, 3.4%), and nausea (n=1, 3.4%). Two patients in the placebo group had nausea (n=2, 6.2%). It was associated with dizziness in one of them, which led to withdrawal. The frequency of patients with at least one adverse event in the prednisolone group (n=5) was significantly higher than in both the itraconazole (n=1) and placebo (n=2) groups (Fisher's exact test, both p<0.001).

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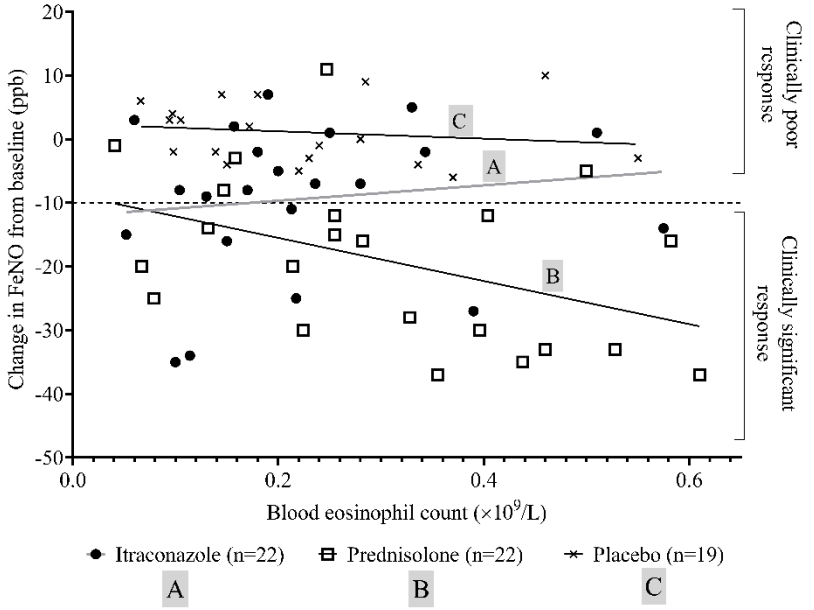

Figure 5. Simple linear regression to predict the change in FeNO according to baseline eosinophil counts in each treatment group.

A greater than 10-ppb reduction in post-treatment FeNO compared to the baseline value was considered a significant anti-inflammatory response. There was no correlation in the itraconazole (r= 0.136, *p*=0.54) or placebo (r=0.152, *p*=0.53) groups. However, a weak negative correlation between baseline blood eosinophil count and change in FeNO was observed in the prednisolone group (r=0.335, *p*=0.042).

Table 3. Comparison of pulmonary function tests in severe persistent asthma treated in three different groups

		FEV1 (L)	FEV1/FVC (%)	FEF_{25-75} (L/S)
Itraconazole	Baseline	1.89 ±0.48	60.3 ±14.6	1.12 ±0.33
	After treatment	2.01 ±0.55	64.8 ±15.2	1.29 ±0.37
	Mean difference	−0.11	−4.4	−0.163
	p value	<0.001	<0.001	<0.001
Prednisolone	Baseline	1.93 ±0.77	62.7 ±15	1.18 ±0.41
	After treatment	2.15 ±0.72	66.4 ±14.1	1.28 ±0.35
	Mean difference	−0.22	−3.7	−0.093
	p value	<0.001	0.007	0.003
Placebo	Baseline	1.83 ±0.58	58.8 ±17.5	1.06 ±0.32
	After treatment	1.81 ±0.6	58.2 ±17.1	1.05 ±0.33
	Mean difference	−0.019	0.62	0.016
	p value	0.46	0.66	0.37

Values are presented as mean±standard deviation.

FEF_{25-75}, forced expiratory flow at 25–75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

DISCUSSION

In this study, long-term treatment of SPA patients with itraconazole led to a significant reduction in RB1 wall thickness and wall area. Consequently, significant increases in airway lumen caliber (IR/BSA and LA/BSA) were discovered. Also, itraconazole treatment led to encouraging improvements in clinical findings and pulmonary function tests. Limited publications could be found about the effect of asthma medications on airway remodeling. Our previous clinical trial revealed that long-term treatment with azithromycin (250 mg, bid, 3 days a week) did not reduce RB1 wall thickness.[22]

The observed itraconazole effect on airway wall thickness could be due to multiple mechanisms:

1) Itraconazole might change the airway structure via its antifungal activity. Itraconazole's antifungal effect is attributed to its ability to inhibit the fungal C-14a demethylase, which terminates the biosynthesis of ergosterol, an essential component of the fungal cell wall membrane.[23] Fungi present in the air can germinate and colonize the host respiratory tract and become a permanent source of toxins, enzymes, and allergenic proteins.[24] Concurrently, long-term use of ICS in patients with SPA provides a permissive environment for fungi to colonize the airways.[7] Therefore, in these asthmatic subjects, colonized fungi initiate an inflammatory and immunological response that may no longer respond appropriately to ICS treatment, a condition that simulates SPA. Furthermore, cytokines released from the involved inflammatory cells promote the release of growth factors from airway epithelial cells, which induce airway remodeling.[8,9] Thus, the decreased fungal burden caused by long-term itraconazole treatment, which was associated with a significant reduction of FeNO, might have reduced both airway remodeling and the associated inflammatory response.

2) Itraconazole can reduce angiogenesis, as an essential component of airway wall remodeling, by different mechanisms. Chong et al. were the first to demonstrate itraconazole's potent ability to inhibit endothelial cell proliferation and other growth factors involved in angiogenesis.[25] Preclinical research has revealed that itraconazole's anti-angiogenic activity is mainly based on its ability to inhibit the VEGFR2 and mechanistic target of rapamycin (mTOR) signaling, which eventually prevents cell migration, chemotaxis, and tube formation.[26-28] Notably, drugs targeting VEGF, mTOR, and angiogenesis are attracting much attention for the treatment of respiratory disorders.[29]

3) Sonic hedgehog (Shh) is a member of the hedgehog gene family with essential roles in embryonic development and the development of different types of cancers.[30] Recent findings revealed that the Shh has also been implicated in airway remodeling of asthma and chronic obstructive pulmonary disease patients by affecting airway epithelial cell differentiation, fibrogenesis, goblet cell metaplasia, and induction of human bronchial smooth muscle cell migration.[31,32] On the other hand, it has been shown that itraconazole can induce apoptosis and cell cycle arrest via inhibiting the Shh pathway in different cancers by a mechanism distinct from its inhibitory effect on fungal sterol biosynthesis.[33] Although the effect of itraconazole in inhibiting the Shh pathway in patients with asthma has not been studied yet, it could be a probable mechanism of WT/BSA reduction in itraconazole-treated subjects of our study.

Apart from the change in RB1 dimensions, this clinical trial revealed that itraconazole was effective in improving the ACT score, severity of dyspnea, FeNO, lung function tests, and reducing asthma exacerbation rates in patients with SPA. Although prednisolone was also influential in improving pulmonary function tests and ACT scores, it was associated with significantly more side effects than itraconazole. The observed improvement in pulmonary function tests and ACT scores of itraconazole- and prednisolone-treated subjects could be attributed to the significant increase in their airway lumen caliber. Although no clinical research has been done on itraconazole in severe asthma, a few publications about the effect of antifungal treatment in severe asthma with fungal sensitization (SAFS) and ABPA are available. A retrospective cohort study revealed that SAFS and ABPA patients who had received antifungal therapy for at least 6 months had a significant increase in FEV1.[15] Denning et al. reported that 32 weeks of oral itraconazole treatment (200 mg, bid) in SAFS patients resulted in significant improvements in quality of life and morning peak flow, whereas FEV1 did not change significantly compared to the placebo group.[14] Agarwal et al. reported that time to first exacerbation after a 6-week treatment of ABPA patients was similar in the itraconazole and prednisolone groups (mean=437 vs. 442 days), which was in line with

our results revealing that there is no statistically significant difference in time to first exacerbation among our treatment groups.[34] However, we should bear in mind that in this study, all SPA subjects entered the study irrespective of the results of sensitivity tests to Aspergillus or other fungi.

The present study has some limitations. As taking lung biopsies is invasive and associated with a high risk in subjects with SPA, the RB1 was assessed using only lung HRCT. Moreover, given that our findings are based on a limited number of patients, the results from such analyses should be used with caution. Nevertheless, this clinical trial is the first step towards expanding our knowledge about the effect of itraconazole on airway remodeling. Further investigations using larger sample sizes and cytokine assay methods to investigate the change of cytokines related to remodeling in the sputum of SPA patients are recommended.

The prescription of prednisolone in SPA is becoming more limited due to the novel target therapies against IgE, IL-5, and IL-4. However, if fungi have a role in asthma resistance, it may be prudent to eliminate these confounding factors before starting nonspecific anti-inflammatory agents because the fungal disease involved in SPA may inhibit optimum results even with the new medications.

This clinical trial revealed that itraconazole could effectively reduce the bronchial wall thickness and wall area and improve clinical findings and pulmonary function tests in SPA. Therefore, we believe that a place for antifungal therapy, especially with itraconazole, can be considered before step 5 of asthma therapy. However, its indications for achieving the best results shall be identified.

STATEMENT OF ETHICS

This clinical trial has been approved by the Iranian Registry of Clinical Trials (IRCT20091111002695N9) and the National Committee for Ethics in Biomedical Research (IR.IAU.MSHD.REC.1398.030).

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None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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