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Effect of Zafirlukast on improving lung function in patients with chronic obstructive pulmonary diseases

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Abstract

Background: There is little evidence about the role of Zafirlukast (a highly selective LTD4 antagonist) in Chronic Obstructive Pulmonary Disease (COPD). The Zafirlukast can reduce the need for short-acting rescue β2 agonists, produce fewer exacerbations of asthma and increased quality of life as possible benefits treatment for asthma. The aim of our study was to evaluate the effects of Zafirlukast improvement of lung function in patients with COPD.

Methods: Twenty five patients with moderate to severe COPD, in stable phase of the disease, participated in this interventional, quasi-experimental study. All patients were received 40*mg* oral Zafirlukast per day for 2 weeks. Pulmonary function Test was performed both at the baseline and at the end of the study. Data were analyzed with paired t-test using SPSS v.16.

Results: The mean age of the patients was 67.29 (SD=5.56) years with the mean baseline for forced expiratory volume in first second (FEV_1) equal to 41.79% (SD=14.96) of predicted value. After 2 weeks, the mean improvements in forced vital capacity (FVC), FEV_1 and FEV_1/FVC were 4.75% (SD=13.18), 3.71% (SD=9.19) and 9.33(SD=27.08), respectively. Zafirlukast produced a non-significant ($p>0.05$) bronchodilation, with maximum mean increase in FEV_1 of 0.04 lit (3%) above baseline.

Conclusion: Results showed that Zafirlukast has no considerable bronchodilatory effect in COPD. Present study consisted of a very short treatment period and it is possible that the extension of this period could possibly have more effects. Additional larger studies are needed to verify the impact of leukoterien receptor antagonists on improving the lung function in COPD patients.

Keywords: Chronic obstructive pulmonary disease (COPD), Pulmonary Function Test, Zafirlukast.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease; its pulmonary component is characterized by airflow limitation that is not fully reversible, usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (1). It is associated with high morbidity and mortality. The primary physiological abnormality in COPD is an accelerated decline in the forced expiratory volume in first second (FEV1). FEV1 declines approximately 30 ml per year in adults over

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30 years of age, in COPD the rate of decline increased to nearly 60 ml per year.

According to guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) the airflow limitation in COPD is characterized by a FEV1 value that is less than 80 percent of the predicted normal value and a FEV1/FVC ratio of less than 0.70 (2).

Cysteinyl leukotrienes (Cys-LTs) are proinflammatory mediators derived from arachidonic acid through the 5-lypoxigenase (5-LO) pathway (3). These products cause bronchial smooth muscle contraction, stimulation of mucous production, enhancement of vascular permeability, and recruitment of eosinophils (4-6).

The cysteinyl leukotriene receptor (CysLT) 1 antagonist is a recent drug for the management of chronic airflow limitation. The CysLTs are potent bronchoconstrictors in subjects with asthma, but there is few evidence for the role of these mediators in COPD, although the presence of CysLTs in the sputum of patients with chronic bronchitis has been shown (7- 9).

Zafirlukast is a highly selective LTD_4 antagonist (8). The benefits of antileukotriene therapy (i.e., 5-lipoxygenase inhibition by zileuton45 and CysLT1 blockade by montelukast or Zafirlukast in children and adults with asthma are improved pulmonary function, decreased daytime and nocturnal symptoms, a reduced need for short-acting rescue β2 agonists, fewer exacerbations of asthma, and an increased quality of life (2).

Methods

Patients

Twenty five patients with moderate to severe COPD, in the stable phase of the disease, participated in the study after giving their informed consent. The patients had to fulfill the American Thoracic Society (ATS) criteria for the diagnosis of COPD.

Inclusion criteria were: age more than 40, history of more than 10 pack/year smoking, and patients with moderate to sever of COPD (FEV1: 35%-80%).

Exclusion criteria were: unstable respiratory disease requiring oral/parenteral corticosteroids within the 4 weeks before the study, and upper or lower respiratory tract infection within 4 weeks of the screening visit.

Study Design

This study was performed using an interventional, Quasi -experimental design. Twenty five outpatient suffering from stable COPD received 40 mg oral Zafirlukast per day for 2 weeks in addition to pervious treatments for their diseases. Pulmonary function test has been controlled before and after drug administration period.

Spirometry

The FVC, FEV1 and FEV1/FVC were measured before drug administration and at the end of two weeks period the same parameters were measured again.

The change in FEV1 was the primary outcome in our study for evaluating that bronchodilatory effect of the drug.

Statistical Analysis

The change in FEV1 was the primary outcome in our study to show bronchodilatory effect of the drug. Pulmonary function Test was performed both at the baseline and at the end of the study. Data were analyzed using SPSS v.16. Based on normal or non-normal distribution of the continuous measurements either Paired sample T-test or Wilcoxon rank test was performed, respectively. In all analytic procedures, a p-value of <0.05 was statistically considered significant.

Results

The mean age of the patients was 67.29 (SD=5.56) years with the mean baseline FEV_1 equal to 41.79% (SD=14.96) of predicted value. After 2 weeks, the mean improvements in FVC, FEV_1 and FEV_1/FVC were 4.75% (SD=13.18), 3.71% (SD=9.19) and 9.33 (SD=27.08), respectively.

Table1. Spirometric characteristic of patients before and after treatment.

Index	Mean±SD		p value
	Before therapy	After therapy	
FEV_1(liter)	1.01±0.33	1.05±0.35	>0.05
FEV_1(%)	41.79±14.96	43.12±19.40	>0.05
FVC(liter)	1.44±0.47	1.56±0.51	>0.05
FVC(%)	53.04±14.65	57.79±19.31	>0.05
FEV_1/FVC	58.96±14.39	68.29±30.14	=0.033

The Zafirlukast produced a non-significant (p>0.05) bronchodilation, with maximum mean increase in FEV_1 of 0.04 lit (3%) above baseline. Table 1 shows spirometric characteristic of patients before and after treatment. However, Wilcoxon test showed that the mean ratio of FEV_1/FVC was significantly improved after two weeks of treatment [58.96% (SD=14.39) vs. 68.29% (SD=30.14), p=0.033]; while other changes were not statistically significant (p>0.05).

Discussion

The role of leukotriene-receptor antagonists is not well recognized in COPD. Patients with rhinitis, asthma, mixed pattern of asthma and COPD might benefit from this drug. The most relevant leukotriene in COPD is leukotriene B_4, which is not inhibited by pranlukast, montelukast or Zafirlukas. The Zileuton might have some inhibitory effect, which has not been studied (11).

Arachidonic acid is the precursor of fatty acid that transformed into the leukotrienes by the 5-lipoxygenase pathway. The leukoteriens exert their biologic activities via binding to and activating specific receptors. Two subtypes of cysteinyl leukoteriens have been identified. Most of cysteinyl leukoteriens actions are mediated by type 1 receptor.

Activation of this receptor leads to smooth muscle contraction in airways, chemotaxis and increased vascular permeability (9). The leukotriene receptor antagonists dilate the airways in the lung with baseline bronchoconstriction.

The CysLTs are portent bronchoconstrictors in subjects with asthma, but there is no rigid evidence for a role of these mediators in COPD, although the presence of CysLTs in the sputum of patients with chronic bronchitis has been documented (7). There are few studies that show the zafirlukast has bronchodilator effect in COPD and cysteinyl leukotrienes might contribute to the bronchospasm in these patients. Cazzola and his group studied 16 patients with COPD and 10 asthmatics in which all were treated with monotherapy of Zafirlukast 40 mg bid, Salmeterol, the combination of Salmeterol and Zafirlukast, or placebo. Pulmonary functions test were measured at 30, 60, 120, 180, and 240 min. At the end of 4 h, salbutamol was administered, and spirometry was repeated in 30 min. In patients with COPD and asthma maximum bronchodilation was seen at 120 and 180 min respectively. Salmeterol increased the FEV_1 by 21.7%, while Zafirlukast increased it by 11.2%. The Zafirlukast produced no acute bronchodilation compared to the effect of Salmeterol alone, but 7 of 16 patients with COPD and 7 of 10 patients with asthma had additional benefit after the first few hours of treated with the combination of Salmeterol and Zafirlukast. The Salbutamol produced no additional increase after patients received Salmeterol or the combination, but there was an increase after Zafirlukast and placebo (12).

Another study by Cazzola et al showed that Zafirlukast improves lung function in smokers with COPD. Sixteen outpatients with stable COPD received 40 mg of oral Zafirlukast. Lung function was measured at 30, 60, 120, 180, and 240 min. At the end of this period, 400 μg of salbutamol was administered to them. The Zafirlukast add-

ed a significant bronchodilator effect between 30 min and 4 h following administration, with a maximum mean increase of 0.134 L above baseline after 2 h. Nine of the 16 patients had an increase in FEV_1 of at least 15% above baseline after Zafirlukast treatment. There was no difference in the post-salbutamol FEV_1 after placebo or Zafirlukast (7).

Nannini LJ Jr et al studied through a randomised, double-blind, crossover and placebo-controlled study and assessed the short-term effects of Zafirlukast in patients with severe COPD. They enrolled 23 subjects, after baseline spirometry, a single oral dose of 40 mg Zafirlukast or the corresponding placebo was administered. FVC and FEV1 was measured every 30 min until 2 hrs. On Zafirlukast day, the mean FEV1 at 90 min and the mean FVC at 90 min were significantly higher than the respective means at placebo day (8).

In a retrospective cohort study to determine the effects of long-term treatment with montelukast on patients with moderate to severe COPD, a significant improvement was observed in complaints of shortness of breath, sputum production, wheezing and nocturnal symptoms during the observation period. In addition, there was a significant reduction in the number of visits to the emergency department, number of hospitalizations and duration of hospitalizations for acute exacerbations of COPD but no significant changes in FEV1 (% predicted), FEV1/FVC ratio (% predicted) and peak expiratory flow rate were found during this time(13). In another study to investigate the short-term effects of montelukast in stable patients with moderate to severe COPD in a randomized, prospective, single-blind, and controlled study, a significant improvement found in vital capacity, FVC, FEV1, dyspnea score and quality of life . These results suggest that leukotriene-receptor antagonists may be taken into account when there is need for an additional anti-inflammatory treatment in COPD patients (14).

This study was performed to evaluate the effect of Zafirlukast on lung function improvement in patients suffering from COPD. The study results showed that Zafirlukast has no bronchodilatory effect in COPD and did not confirm the hypothesis that Zafirlukast improves lung function in COPD, it seems that adding this drug may improve treatment such as those available as bronchodilators without more benefit. But we had many limitations in our study; one was the sample size. Because of methodological and financial reasons we had to use small sample size. The present study was an observation of a very short period of drug impact but it is possible that if we extend duration of study, the result could have been different.

Nevertheless, larger samples are needed to verify the impact of leukoterien receptor antagonists on the improvement of lung function in COPD patients.

Conclusion

Results showed that Zafirlukast has no considerable bronchodilatory effect in COPD. Our results showed that Zafirlukast had no considerable bronchodilatory effect in COPD except for FEV1/FVC. Demonstrated effects of Zafirlukast were mostly observed in asthma; and its results in COPD are still controversial. There are a few studies that show Zafirlukast has bronchodilator effect in COPD and cysteinyl leukotrienes might contribute to the bronchospasm in the patients. Present study consisted of a very short treatment period and it is possible that the extension of this period could possibly have more effects. Additional studies are needed to verify the impact of leukoterien receptor antagonists on improving the lung function in COPD patients. In conclusion the present study did not confirm the hypothesis that Zafirlukast causes improvement in lung function in COPD patients. Although several studies have shown that Zafirlukast may improve lung function in COPD, however, our study suggests that Zafirlukast has no bronchodilatory effect in COPD.

References

1. Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Executive summary 2006. Global Initiative for Chronic Obstructive Lung Disease (GOLD). http://www.goldcopd.org/ (Accessed on December 14, 2009).

2. Sutherland ER, Cherniack RM. Management of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2004 Jun 24;350(26):2689-97.

3. Riccioni G, Bucciarelli T, Mancini B, Di Ilio C, D'Orazio N. Antileukotriene drugs: clinical application, effectiveness and safety. Curr med Chem. 2007;14(18):1966-77.

4. Busse WW, McGill KA, Horwitz RJ. Leukotriene pathway inhibitors in asthma and chronic obstructive pulmonary disease. Clin Exp Allergy 1999 Jun;29 Suppl 2:110-5.

5. Usery JB, Self TH, Muthiah MP, Finch CK. Potential role of leukotriene modifiers in the treatment of chronic obstructive pulmonary disease. Pharmacotherapy. 2008 Sep;28(9):1183-7.

6. Drakatos P, Lykouras D, Sampsonas F, Karkoulias K, Spiropoulos K.Targeting leukotrienes for the treatment of COPD? Inflamm Allergy Drug Targets. 2009 Sep;8(4):297-306.

7. Cazzola M, Boveri B, Carlucci P, Santus P, Dimarco F, Centanni S, Allegra L. Lung function improvement in smokers suffering from COPD with Zafirlukast, a CysLT(1)-receptor antagonist. Pulm Pharmacol Ther. 2000;13(6):301-5.

8. Nannini LJ Jr, Flores DM,Bronchodilator effect of Zafirlukast in subjects with chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2003; 16(5):307-11.

9. McMillan RM. Leukotrienes in respiratory disease. Paediatr Respir Rev. 2001 Sep;2(3):238-44.

10. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukoterien pathway. N Engl J Med. 1999 Jan 21;340(3):197-206.

11. Donohue JF. Therapeutic responses in asthma and COPD. Bronchodilators.Chest. 2004 Aug;126(2 Suppl):125S-137S; discussion 159S-161S.

12. Cazzola M, Centanni S, Boveri B, Di Marco F, Santus P, Matera MG, Allegra L. Comparison of the bronchodilating effect of salmeterol and Zafirlukast in combination with that of their use as single treatments in asthma and chronic obstructive pulmonary disease. Respiration. 2001;68(5):452-9.

13. Rubinstein I, Kumar B, Schriever C. Long-term montelukast therapy in moderate to severe COPD--a preliminary observation. Respir Med. 2004 Feb;98(2):134-8.

14. Celik P, Sakar A, Havlucu Y, Yuksel H, Turkdogan P, Yorgancioglu A. Short-term effects of montelukast in stable patients with moderate to severe COPD. Respir Med. 2005 Apr;99(4):444-50.