

Zafirlukast Improves Pulmonary Function in Patients with Moderate Persistent Asthma Receiving Regular Inhaled Steroids: A Prospective Randomized Control Study

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Background: Zafirlukast is a leukotriene receptor antagonist that was invented to treat patients with chronic asthma.

Methods: To evaluate whether the zafirlukast improved the peak expiratory flow rate (PEFR) and clinical symptoms, 31 asthmatic patients with moderate persistent asthma who received regular inhaled corticosteroid were randomly divided into the study group (N=17). They received the zafirlukast 20 mg bid for 4 weeks, and the control group (N=14) received a placebo. Daily morning and evening PEFR and St. George's Respiratory Questionnaire (SGRQ) scoring were recorded respectively. The levels of serum IgE and urine leukotriene E₄ before and after treatment were measured using enzyme linked immunosorbent assay and enzyme immunoassay kits.

Results: In the zafirlukast treated group, the morning PEFR was significantly improved from 314.4 ± 20.6 to 340.6 ± 18.3 L/min (N=17, $p < 0.05$) after 4 weeks of treatment, while the control group did not show any significant changes. The zafirlukast group had significant improvement in their symptom scores of SGRQ from 48.6 ± 4.6 to 33.8 ± 4.7 (N=17, $p < 0.05$). However, the placebo did not improve the symptom scores.

Conclusion: Leukotriene receptor antagonists effectively improved symptoms and benefited lung function for moderate persistent asthmatic patients who had received regular treatments with inhaled steroids.
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Key words: peak expiratory flow rate; St George's respiratory questionnaire; leukotriene.

The cysteinyl leukotriene (LT) C₄, LTD₄, and LTE₄, are produced by LTC₄ synthase from the precursor LTA₄ which is a product of 5-lipoxygenation of arachidonic acid. The LTC₄, LTD₄, and LTE₄ have been implicated in the pathogenesis of asthma.^(1,2)

They have been discovered in increased concentrations from bronchoalveolar lavage fluid and urine of patients with asthma. LT plays an important role in bronchial smooth muscle proliferation and constriction. It also increases bronchial secretion,

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local inflammation, and enhances eosinophil migration.⁽³⁻⁵⁾ Evidence for the role of LT in the pathogenesis of asthma has been provided by study results in which anti-leukotriene drugs blunted the magnitude of bronchoconstriction caused by exercise, allergen challenge, cold-air hyperventilation, and administration of non-steroid anti-inflammatory drugs to sensitized subjects.^(6,7)

Zafirlukast is a leukotriene receptor antagonist that blocks the LT 1 receptor on the smooth muscle and other hematopoietic cells. It inhibits the bronchoconstriction effect of LT that is released from mast cells and eosinophils.⁽⁸⁻¹⁰⁾ Long-term clinical trials with anti-leukotriene drugs have been reported to improve pulmonary function, decrease asthma symptoms and the need of rescue β_2 -agonists, and reduce asthma exacerbations predominantly in patients with moderate to severe asthma. Several studies have shown the anti-inflammatory effects of leukotriene receptor antagonists, but they were not as effective as inhaled corticosteroids.⁽¹¹⁻¹⁴⁾ In patients with moderate to severe persistent asthma, leukotriene receptor antagonists are considered as add-on therapy with inhaled corticosteroid and may allow for the decrease in the dosage of corticosteroid because of different mechanisms.^(15,16) This study was designed to investigate whether zafirlukast might be of benefit in patients with moderate persistent asthma undergoing regular inhaled corticosteroids treatment.

METHODS

Study design

The study was designed as a randomized double blind control trial. The Chang Gung Memorial Hospital Ethics Committee approved the study protocol.

Patients

Patients eligible to enter the trial were adults 18 to 75 years of age diagnosed with moderate persistent asthma for at least 6 months according to the American Thoracic Society criteria.⁽¹⁷⁾ The eligibility requirements included a forced expiratory volume in 1 second (FEV₁) within prediction of 60% to 80%, a reversibility in measurements of peak expiratory flow rate (PEFR) or FEV₁ \geq 12% after inhalation of 400 μ g albuterol, and current therapy with inhaled

corticosteroids (budesonide \geq 400 μ g/day or equivalent). None of the patients had history of other significant respiratory diseases or respiratory tract infections preceding entry into the study, or had been hospitalized with asthma within 3 months prior to enrollment in the study. All of them had not smoked during the 6 months preceding enrollment. The patients did not receive any anti-leukotrienes or cromolyn or nedocromil 3 weeks before entry in the study. No long-acting anti-histamines or aspirin or long acting β_2 agonist were used during the week before the study. Written informed consent was obtained from all patients.

Study protocol

During a 2-week pre-randomization (baseline) period, the patients were maintained on their existing inhaled corticosteroid therapy and supplemental short-acting β_2 -agonist bronchodilators. Then the eligible patients were randomized to 4 weeks of treatment with either 20 mg of zafirlukast or a matching placebo taken twice daily in addition to their existing therapy, which remained unchanged from that taken at study entry. When the asthma was being insufficiently controlled during the study period and required a change in a patient's medication, the responsible physician was allowed to withdraw the patient from the study or to provide any additional asthma therapy considered necessary.

At the first visit, the patients' demographic details were recorded and their inhaler techniques were assessed. During both the baseline and treatment periods, patients were instructed to record the best of three consecutive measurements of daily morning and evening PEFR at home, using a peak flow meter (mini-Wright; Clement Clark International, Harlow, UK). Morning PEFR was the primary outcome measurement used in this study. Patients were also asked to record their asthma diary, including their daytime asthma symptom score, number of awakenings with asthma each night, mornings with asthma on arising, and number of puffs of supplemental short-acting and β_2 -agonist used each day. Patients' FEV₁ and PEFR were also measured in the clinic, at least 6 hours after the last dose of β_2 -agonist, at the beginning and end of the baseline period, and after 4 weeks of treatment during the study. At each visit, changes in medication, adverse events, and asthma exacerbations were recorded.

Quality of life (QOL) was measured before the first dose of study medications and at the end of the treatment period by the validated St. George's Respiratory Questionnaire (SGRQ).^(18,19)

Compliance with tablet medication was assessed by the return of blister packs. The total number of empty blisters was expressed as a percentage of the total number of prescribed tablets to be taken. Patients continued to use their own inhaled corticosteroid medication during each period of the study. The venous blood and urine were collected before and after the study period.

Asthma exacerbations

Exacerbations of asthma that required emergency room treatment or hospitalization, or that resulted in death, were classified as severe. Exacerbations of asthma that required additional controller therapy, such as oral steroids, an increase in the daily dose of inhaled corticosteroids, or addition of a long acting bronchodilator or theophylline were classified as moderate, as were asthma exacerbations that the investigators judged to be severe or moderately severe adverse events. An asthma-related adverse event classified as being of mild severity, a deterioration in asthma control defined as a decrease in clinically measured FEV₁ of $\geq 20\%$ from the baseline FEV₁, or a deterioration in asthma control recorded by the clinician at the clinic visit, but not documented as an adverse event, qualified as a mild exacerbation. All patients who experienced moderate to severe asthma exacerbations were excluded from the study because of the great variability in FEV₁ and PEFr.

Leukotriene E4 measurements

Urine samples were collected before and 4 weeks after treatment began. The levels of LTE₄ in

the urine samples were measured using commercially available enzyme linked immunosorbent assay kits.

Total IgE

Twenty ml of venous blood were spun down and the sera were stored before the analysis for total IgE using Pharmacia Cap system.

Statistical analysis

All asthma diary card variables and pulmonary function between groups were assessed using repeated measures ANOVA and paired t test. When the data presented without normal distribution, a non-parametric analysis was subsequently performed using Wilcoxon test (two-tailed). Data are presented as mean \pm SD. A *p* value less than 0.05 was considered to be significant.

RESULTS

Eligible patients were randomized to receive either zafirlukast (N=20) or placebo (N=18). The demographic details of the two groups are summarized in Table 1. There were no significant differences in gender or age between the two groups. The values of pulmonary functions and morning PEFr and the dose of inhaled corticosteroids of the two groups before entry were broadly similar. A total of seven patients (3 in the zafirlukast group and 4 in the placebo group) were withdrawn from the study protocol because of acute asthma exacerbations which required emergency room visits.

Morning PEFr significantly increased from the baseline by 27.1 ± 2.1 L/min (N=17, *p* < 0.01) after 4 weeks of treatment in the zafirlukast treated group (Fig. 1A). There was also a significant improvement in evening PEFr by 19.4 ± 3.4 L/min (*p* < 0.01) after

Table 1. Demographic Characteristics of Patients

	Inhaled corticosteroids+ zafirlukast (N=17)	Inhaled corticosteroids+ placebo (N=14)
Gender, male/female	9/8	7/7
Age	58.6 \pm 3.0 (29-75)	56.9 \pm 2.8 (39-70)
FEV ₁ , L	1.85 \pm 0.1 (1.09-2.39)	1.86 \pm 0.08 (1.20-2.29)
FEV ₁ , % predicted	67.8 \pm 1.4 (61-79)	69.1 \pm 1.4 (62-77)
Morning PEFr, L/min	313.5 \pm 21.8 (180-440)	321.4 \pm 17.0 (230-420)
Daily corticosteroids (budesonide) dose, μ g	1141.2 \pm 38.6 (800-1600)	1168.4 \pm 42.5 (800-1600)

Abbreviations: FEV₁: forced expiratory volume in one second; PEFr: peak expiratory flow rate.

Data are mean \pm SD. The range of the data is presented in parentheses.

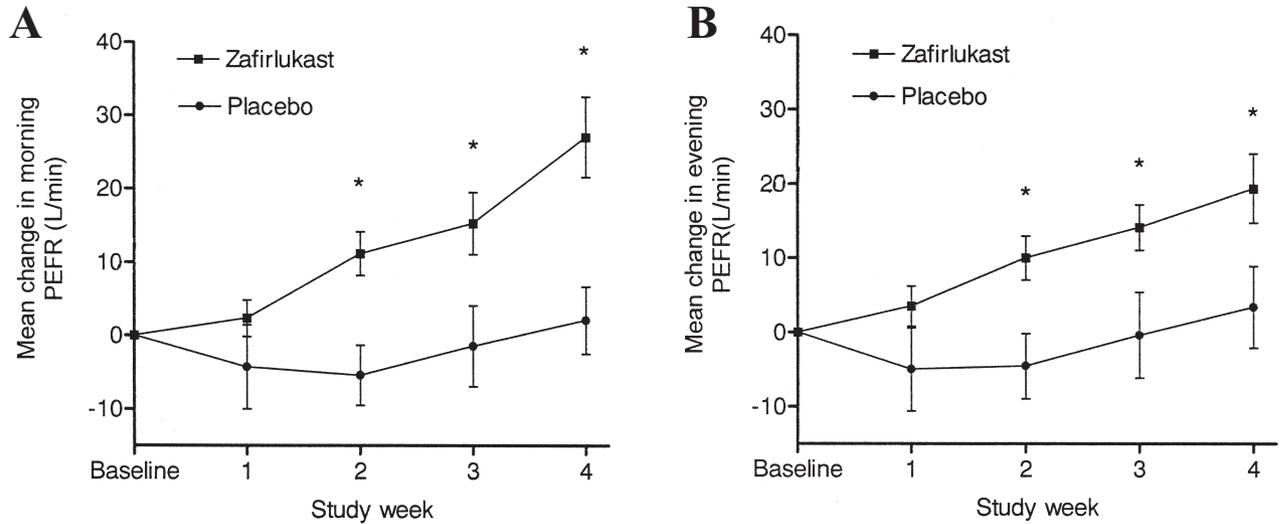


Fig. 1 Changes in PEFR in patients treated with inhaled corticosteroids plus zafirlukast at 20 mg twice daily (close square) or with inhaled corticosteroids plus placebo (close circle). The changes from baseline for morning PEFR (A) and evening PEFR; (B) measured daily by patients are presented as the weekly least-squares mean values. The data are present as mean \pm SD * p <0.01 compared to the baseline.

4 weeks of treatment with zafirlukast (Fig. 1B). However, in the control group, the morning PEFR and the evening PEFR at the end of study only slightly increased by 1.4 ± 4.7 L/min and 3.4 ± 5.4 L/min, respectively (Fig. 1A and 1B).

QOL was assessed before and at the end of the treatment period and the mean absolute SGRQ total score and subscores are reported in Table 2. After 4 weeks of treatment, patients that received zafirlukast showed a statistically significant improvement in symptom score and activity score. In the placebo group, a significant difference was observed only in the activity score.

The level of total serum IgE before and after the study did not show any statistical differences either in the zafirlukast group or the placebo group. In the zafirlukast treated group, the serum total IgE was 222.3 ± 57.9 KU/L at baseline and 225.5 ± 57.1 KU/L after treatment. In the placebo group, the serum total IgE was 321.4 ± 17.0 KU/L at baseline and 323.6 ± 15.9 KU/L at the end of the study. The urine leukotriene E4 concentrations were highly variable among patients. There were no significant differences after treatment in the zafirlukast group (2130.5 ± 335.1 to 1870.4 ± 306.5 pg/ml $p=0.51$, N=17) and the placebo group (1491.1 ± 266.2 pg/ml to 1445.0 ± 238.5 pg/ml, $p=0.25$, N=14).

Table 2. Scores of St. George's Respiratory Questionnaire before and after Treatment

	Baseline	4 week treatment
Zafirlukast group		
Symptom Score	48.6 ± 4.6	$33.8 \pm 4.7^*$
Activity Score	35.2 ± 5.7	$27.2 \pm 5.0^*$
Impact Score	30.0 ± 3.5	25.2 ± 3.9
Control group		
Symptom Score	46.2 ± 5.4	37.1 ± 5.1
Activity Score	40.2 ± 6.4	$28.6 \pm 5.6^*$
Impact Score	30.4 ± 4.3	24.8 ± 4.7

Data are presented as mean \pm SD. * p <0.05 compared to the baseline of corresponding group.

DISCUSSION

The results of our study demonstrated that for asthmatic patients, whose symptoms persisted despite regular treatment with inhaled corticosteroids, the addition of zafirlukast resulted in a statistically significant improvement in morning and evening PEFR and alleviation of asthma symptoms. These observations strongly suggest that leukotrienes contribute to the pathogenesis of moderate to severe asthma even after the use of inhaled corticosteroids, and the addition of a leukotriene-receptor antagonist improved asthma control in patients with more

severe asthma.

In our study, seven patients were excluded from our protocol due to acute exacerbation. For patients with moderate persistent asthma, acute exacerbation is not uncommon because of airway hyperresponsiveness and instability. The reason we excluded these patients was due to the great variability in daily PEFr during the period of acute exacerbation and it was difficult to use one single PEFr data to represent the actual asthma condition.

In our study, the QOL for both groups showed significant improvement in activity score of SGRQ, but only the zafirlukast group showed significant progress in symptom score. In patients with moderate persistent asthma, good compliance to inhaled corticosteroids usually predicts better asthma control. In our study, patients were asked to record their asthma diary cards, which were returned to our clinics every 2 weeks. The improvement of activity score in both groups may be due to the strict follow-up rule. The improvement of symptom score in the zafirlukast group implied that the drug provided additional benefits for the control of asthma symptoms.

Inhaled glucocorticoids are considered the first-line treatment for patients with moderate-to-severe, persistent asthma. However, many patients taking inhaled glucocorticoids continue to have symptoms and need additional treatment. The specific findings of these patients include considerable impairment of QOL, evidence of bronchodilator-resistant pulmonary functions with small residual volume to total lung capacity ratio, elevated neutrophil levels in sputum, elevated nitric oxide levels in peripheral blood, and increased excretion of eosinophil peroxidase and leukotriene E₄.⁽²⁰⁾ Of particular importance was the persistence of eosinophils and neutrophils in sputum despite the use of high-dose inhaled or systemic corticosteroids. These observations suggest that lingering regions of inflammation may remain beyond the reach of current inhaled steroid formulations. The leukotriene receptor antagonists have been shown to reduce eosinophil counts in peripheral blood,⁽²¹⁾ sputum, and bronchoalveolar lavage fluid, suggesting these drugs have anti-inflammatory properties.⁽³⁾ The results of our study demonstrated that zafirlukast further improved the persistent pulmonary function impairment in asthmatic patients with regular inhaled steroid treatment, indicating leukotrienes may contribute in part to the residual airway inflammation in

these patients.

Patients with allergic airway diseases are commonly sensitized to multiple allergens.⁽²²⁾ These patients might have an enhanced IgE immune responses, as shown by higher serum levels of total and specific IgE.⁽²³⁾ The changes of serum IgE levels may reflect the partial disease control of asthma. Our results did not show any significant changes in serum IgE after treatment with zafirlukast. It seems that modulating the IgE immune responses does not exert clinical effects.

Zafirlukast is a competitive antagonist of the LT₁ receptor. Our results reveal no significant changes in the urinary LTE₄ concentration after treatment with zafirlukast which suggests it does not influence the synthesis or metabolism of leukotriene. Patients with aspirin-intolerant asthma are indeed known to have increased production of cysteinyl-leukotrienes,^(24,25) and this may be due to upregulation of the LTC₄ synthase and genetic predisposition.^(26,27) Zafirlukast has been reported to be beneficial in these patients.⁽¹⁰⁾

There was a similar study reported by Virchow et al.⁽²⁸⁾ In their study, the efficacy of high dose zafirlukast (80 mg twice daily) with inhaled corticosteroid compared with inhaled corticosteroid alone was evaluated and significant PEFr improvement and reduction of acute exacerbation was discovered. Compared with their study, our study demonstrated that even low doses of zafirlukast (20 mg twice daily) provided good control for patients with moderate persistent asthma. No drug related side effects were found in the low dose zafirlukast study.

In conclusion, zafirlukast improved the morning and evening PEFr and clinical symptoms of asthmatic patients who had received regular inhaled corticosteroids. For patients with moderate persistent asthma, leukotriene antagonists may be useful as adjunct therapy to decrease the dosage of inhaled steroids.

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Zafirlukast 對規律使用吸入性類固醇的中度持續性氣喘病人的肺功能的改善：一個前瞻性的隨機控制研究

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背景： 白三烯素接合器的拮抗劑已經被研發用來治療慢性氣喘。

方法： 本篇研究在探討Zafirlukast是否會改善氣喘病人的尖峰吐氣流速值和臨床症狀。31位固定使用吸入型類固醇的中度持續性氣喘的病人被隨機分配成實驗組(17位病人)和對照組(14位病人)，實驗組接受四週的Zafirlukast，每天兩次一次20毫克，對照組則接受吸入型類固醇和安慰劑，每天清晨和傍晚的尖峰吐氣流速值，治療前後的聖喬治呼吸評量表，血清當中的免疫球蛋白E和尿液中的白三烯素E4被測量來評估治療效果。

結果： 經過四個星期的治療，在實驗組清晨的尖峰吐氣流速值明顯的由 314.4 ± 20.6 進步到 340.6 ± 18.3 公升/分鐘，而對照組則沒有明顯的改變。在實驗組中病人的聖喬治呼吸評量表的症狀分數也有明顯的改善從 48.6 ± 4.6 到 33.8 ± 4.7 ，而對照組則沒有明顯的差別。

結論： 白三烯素接合器的拮抗劑對於已經規律使用吸入型類固醇的中度持續性氣喘病人的尖峰吐氣流速值和臨床症狀可以有明顯的改善。
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關鍵字： 尖峰吐氣流速值，聖喬治呼吸評量表，白三烯素。

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