

The Zafirlukast Clinical Experience in Patients with Mild to Moderate Asthma

—An Open, Non-Comparative Study—

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ABSTRACT

BACKGROUND: Zafirlukast is an oral antileukotriene used in the treatment of patients with asthma. To investigate its efficacy and safety in a clinical setting, we evaluated zafirlukast in patients with mild to moderate asthma.

METHODS: An open, non-comparative study was carried out. A total of 32 patients who visited our outpatient department of Kaohsiung Medical University Hospital were enrolled. Each enrolled patient must meet our inclusion criteria for symptoms and/or reversibility and/or the FEV₁ predicted value in screening period. Patients were observed during a screening period of one to two weeks and received zafirlukast 20 mg twice daily for a period of 6 weeks. Peak expiratory flow (PEF) was measured twice a day, and overall asthma symptom scores, number of nighttime awakenings, severity of morning symptoms and use of β_2 -agonist were recorded daily. The means of changes from baseline to each follow-up visit and endpoint were evaluated by ANOVA.

RESULTS: The mean age of thirty-two patients (13 males, 19 females) was 34.34 ± 1.50 (range: 19-52). In the efficacy analysis, all parameters (including: FEV₁, PEF, daytime changes of asthma symptom score, nighttime awakening) showed statistically significant improvement that continued throughout 6 weeks of this study period. More than 90% of both physicians and patients indicated clinical improvement in pulmonary measures as well as in asthma symptoms. In the safety analysis, our results indicated that there were no statistically significant liver and renal functional changes between screening phase and endpoint visit. No serious adverse event was observed in this study.

CONCLUSIONS: We conclude that zafirlukast 20 mg twice a day is well tolerated and improves pulmonary function and asthma symptoms in patients with mild to moderate asthma.

Key word: antileukotriene, Zafirlukast, asthma.

INTRODUCTION

Asthma is characterized by airway obstruction, inflammation, and heightened

airway responsiveness to a variety of stimuli. Successful long-term management of asthma involves the application of anti-inflammatory medications, such as corticosteroids and cromones, to control symptoms⁽¹⁻³⁾. Most current therapies for asthma are inhaled regimens. However, many asthma patients receiving these drugs still suffer from considerable morbidity.

Leukotriene receptor antagonists, a new generation of asthma medications, are being developed because they interfere with the action of leukotrienes^(4,5). Leukotrienes are implicated in bronchoconstriction and the formation of airway edema, which result from the inflammatory process in patients with asthma. Controlled clinical trials^(6,7,8) have demonstrated that antileukotriene-directed therapy produces clinical benefits in asthmatic patients.

The purpose of this clinical trial was to study zafirlukast in a population of asthmatic patients in a clinical setting. We studied the clinical and economic effectiveness of zafirlukast among patients with mild to moderate asthma by means of an open study.

Patients and Methods

The data for this effectiveness study originated from an open, non-comparative clinical design to assess the efficacy of zafirlukast in patients with mild to moderate asthma who were followed up for 6 weeks after the zafirlukast therapy.

Clinical Protocol

Patients were observed prospectively during a one-week screening period. The one-week screening period could be extended by an extra week if needed for patients to meet the criteria for symptoms and/or reversibility and/or the FEV₁ predicted value. Patients who fulfilled the asthma symptom criteria and other inclusion criteria began therapy with zafirlukast 20 mg twice a day. Patients were then followed every 2 weeks for visits 2 and 3 for a total of 6 weeks.

Patients were eligible for this study if they were 16 years of age or older, had no cigarette smoking in the previous 6 months, and had an FEV₁ at least 60% of the predicted value. They had to have a 15% or greater improvement in FEV₁ after the inhalation of a bronchodilator at screening or at any time between screening period. Each patient must be using short-acting inhaled as-needed short-acting inhaled β_2 -agonist only. Patients also had to be symptomatic (defined as a 7 day asthma symptom score ≥ 8) during the run-in period. The asthma symptom score was summed over 7-days of overall assessment of asthma symptoms, which were rated daily by the patient as 0 = none, 1 = mild (no interference with activities), 2 = moderate (interference with some activities), or 3 = severe (interference with many activities). Nighttime awakening was recorded as a yes or no according to whether the patient was awakened during the previous night because of asthma. β_2 -agonist use was recorded as number of puff per day. Patients were observed during one to two week screening period and received zafirlukast 20 mg twice a day for a period of 6 weeks. Each patient performed pulmonary function using the peak flow meter (Clement Clarke Inc., Columbus, Ohio) for peak expiratory flow (PEF) measurement. PEF was measured twice a day, and overall asthma symptom scores, number of nighttime awakenings, severity of morning symptoms and β_2 -agonist use were recorded daily.

Patient's compliance of the oral zafirlukast was assessed at visit three and four.

All blister packs administered by the investigator to the patient will be collected at the treatment visit. A drug count will be performed to verify patient compliance. The patient must have taken at least 80% of their oral medication in order to be considered compliant with the protocol.

Statistical Analysis

The FEV₁, PEF, and diary card efficacy parameters were presented using summary statistics, these consisted of mean and standard error. The means of changes from baseline to each follow-up visit and endpoint were evaluated by ANOVA. All treated patients were included in the analysis of safety. Adverse events were tabulated and incidence rates were calculated.

Results

Forty patients from our outpatient department of Kaohsiung Medical University Hospital were enrolled and 32 patients completed the clinical trial. Of the eight (20%) patients, who failed to complete the trial, four patients were lost to follow-up and four patients decided not to continue in the study. The reasons for withdrawal from the study included worsening asthma in two patients, concurrent illness in one patient, and protocol violation in one patient. Table 1 summarized the demographic information for all enrolled patients.

The efficacy analysis included clinical visit FEV₁, PEF, daytime changes of asthma symptom score, nighttime awakening and β_2 -agonist use. Figure 1 shows the effect of zafirlukast on clinical visit FEV₁. The results indicated that the patients had increment in FEV₁ at every study visit, and the increments remained statistically significant throughout 6 weeks of this study period ($p < 0.05$). Figure 2 shows the effect of zafirlukast on clinical visit PEF and the significant improvement of PEF was observed ($p < 0.001$). More than 90% of both physicians and patients indicated improvement in pulmonary measures.

The descriptive statistics of mean value over 7 days for daytime asthma symptom scores were shown in figure 3. The results for changes from baseline in daytime symptom score showed statistically significant reduction in symptom score at every week and endpoint ($p < 0.001$). Figure 4 shows the sum of night-time awakenings over seven days. The corresponding results for changes in the numbers of night-time awakening from baseline also indicated statistically significant decrements in night-time awakening at every week and endpoint with a p-value of less than 0.014.

In the safety analysis, our results indicated that there were no statistically significant changes in liver and renal function between screening phase and endpoint visit. No serious adverse event was observed in this study except two patients, one had diarrhea (1/32=3.1%) and the other one had headache (1/32=3.1%).

Twenty-nine out of our 32 patients had 100% compliance. Three patients had 97.4%, 94.5%, and 91.5% compliance, respectively.

Discussion

The Global Initiative for Asthma (GINA) was published in 1995 as a collaborative report by the National Heart, Lung and Blood Institute (NHLBI) and World Health Organization (WHO) ⁽¹¹⁾. The purpose of these guidelines is to disseminate and implement the recommendations of the International Consensus Report in all countries where the asthma morbidity and mortality are important public

health problem. In May 1997, the revised USA asthma guidelines were published in the Expert Panel Report II ⁽¹²⁾. The GINA guidelines and the Expert Panel Report II are essentially similar in that they classify asthma severity in different steps based on the parameters of daytime symptoms, night-time symptoms and lung function before treatment. Drugs currently used for the treatment of asthma, such as inhaled corticosteroids and cromones, are well tolerated when used at normal therapeutic doses. It is therefore essential that any new treatment for asthma, such as the leukotriene receptor antagonists, must be equally well tolerated. Antileukotriene drugs are beginning to be incorporated into guidelines for the management of asthma.

Zafirlukast is an oral leukotriene receptor antagonist indicated for the chronic treatment of patients with mild to moderate asthma. Controlled clinical trials designed for regulatory approval have shown that up to 13 weeks of zafirlukast therapy improves pulmonary function parameters, reduces the need for β_2 -agonist rescue medications, and improves overall asthma symptoms when used in patients with mild to moderate ^(7, 8, 9, 13), or severe ⁽¹⁰⁾ asthma. One 13-week trial of zafirlukast also demonstrated improvement in quality of life in patients with moderate reversible airflow obstruction ⁽¹³⁾. In addition, interim results from an open-label extension trial have demonstrated the long-term efficacy and safety of zafirlukast in patients with mild to moderate asthma ⁽¹⁴⁾. The results of this clinical practice study, an open, non-comparative, demonstrate that zafirlukast was effective in treating mild to moderate asthmatic patients. Patients gained significant improvements in both FEV₁ and PEF values, as well as in overall asthma symptoms score, morning asthma symptoms, night-time awakenings, and β_2 -agonist use after the 6 weeks zafirlukast 20 mg twice a day therapy.

An important goal of asthma therapy is the prevention of asthma symptoms and asthma exacerbations. Pharmacological therapy plays a key role in achieving this goal, but noncompliance with treatment plans may undermine potential gains, and may have significant impact on clinical outcome. Efforts to improve compliance are complicated by the finding that many patients do not use correct inhaler technique ⁽¹⁵⁾. It indicated that the full dose of medication may not be delivered, and patients may not derive optimal benefit from therapy ⁽¹⁶⁾. Eighty-five percent of patients in our trial indicated that they preferred oral zafirlukast to other asthma therapies; eighty percent of these patients articulated a preference for oral rather than inhaled medications. Because almost all of patients felt that they were able to comply with dosing regimen, zafirlukast could be an important form of treatment, especially in patients who are less than fully compliant with inhaler therapy. These high levels of compliance with zafirlukast were confirmed in this clinical trial.

Placebo-controlled trials of longer duration than our trial have demonstrated a favorable safety profile for zafirlukast that is clinically indistinguishable from that of placebo ⁽⁷⁻¹⁰⁾. However, Churg-Strauss syndrome has been observed in patients on antileukotrienes ⁽¹⁷⁾. Common adverse events such as mild liver dysfunction, headache, nausea, pharyngitis, and sinusitis are reported. In our safety analysis, there were only two of 32 patients who had diarrhea and headache. Neither liver and renal dysfunction nor serious adverse events was recorded.

Although there are only 32 patients enrolled in this open, non-comparative study, we showed the clinical usefulness and effectiveness of zafirlukast for the treatment of

mild to moderate asthma. We suggest that zafirlukast 20 mg twice a day is well tolerated and can improve pulmonary function and asthma symptoms in patients with mild to moderate asthma. Further long-term studies of the antileukotriene in the treatment of mild, moderate, and severe asthma are need.

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用 Zafirlukast (白三烯拮抗劑) 治療輕度到中度哮喘病人之臨床經驗

— 一個開放性及非比較性的研究 —

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摘要

背景：Zafirlukast 是一種口服的白三烯拮抗劑(antileukotriene)，被用在治療哮喘病人。我們使用 Zafirlukast 治療輕度到中度哮喘病人，並評估它的有效性及安全性。

方法：這是一個開放性及非比較性的研究。我們針對 32 位在高雄醫學大學附屬

醫院門診病人作研究，每位進入研究的病人均合乎收案標準，包括症狀、可逆性及篩選期間肺功能第一秒呼氣容積(FEV1) 測量結果。在篩選期間病人被觀察壹到兩週後，開始服用 Zafirlukast 20 mg 分為一天兩次，共服用六週。服用期間病人必須記錄：每天兩次的尖峰呼氣流速(PEF) 、病人哮喘症狀分數、晚上因哮喘睡醒次數、早晨症狀嚴重度及每天使用乙二型交感神經刺激劑次數。研究之統計是用 ANOVA 方法。

結果：三十二位病例（13 位男性，19 位女性）的平均年齡是 34.34 ± 1.50 歲（從 19 歲到 52 歲）。在有效性分析，每個參數指標（包括：FEV1、PEF、病人哮喘症狀分數、晚上用哮喘睡醒次數、早晨症狀嚴重度及每天使用乙二型交感神經刺激劑次數）在六週治療期間均呈現有有意義的改善。百分之九十以上的醫師及病人都認為臨床上肺功能及哮喘症狀上有改善。有關安全性分析：我們的結果顯示在研究治療期間的肝、腎功能均無影響。而且亦無重大事故發生。

結論：依據我們的研究結果，我們認為服用 Zafirlukast 20 mg 一天兩次對於輕度及中度哮喘病人的治療是有效及安全。

關鍵詞：白三烯拮抗劑(antileukotriene) ，Zafirlukast ，哮喘。

Figure legends

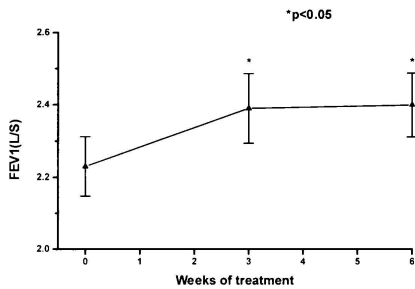


Figure 1. Effect of zafirlukast on clinical visit force expiratory volume in one second (FEV₁) in patients with mild to moderate asthma. (n=32, p<0.05)

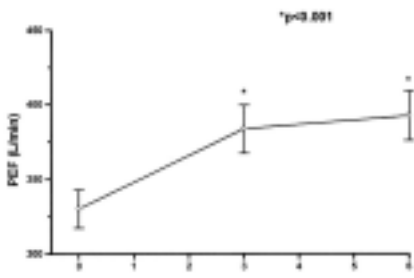


Figure 2. Effect of zafirlukast on clinical visit peak expiratory flow (PEF) in patients

with mild to moderate asthma. (n=32, p<0.001)

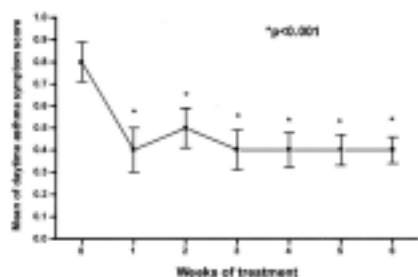


Figure 3. Effects of zafirlukast on daytime asthma symptom score in patients with mild to moderate asthma. (n=32, p<0.001)

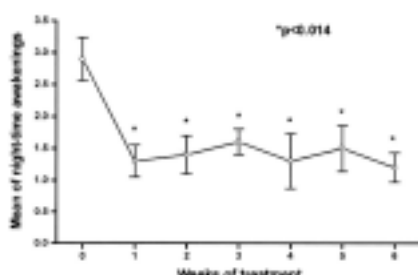


Figure 4. Effect of zafirlukast on night-time awakening in patients with mild to moderate asthma. (n=32, p<0.014)

Table 1. Demographic characteristics of study patients with mild to moderate asthma.

Characteristic	No. of cases
Age, years (mean age \pm SE, range)	(34.34 \pm 1.50, range: 19-52)
<20	2
20-65	30
>65	0
Sex	
Male	13
Female	19
Asthma severity	
Mild	9
Moderate	23
Duration of asthma	
1 to 5	5
6 to 10	13
11 to 20	14
>20	1

SE, standard error