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Roflumilast for asthma: Efficacy findings in non-placebo-controlled comparator and dosing studies☆

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ABSTRACT

Background: Roflumilast, a phosphodiesterase-4 inhibitor, has an established place in the treatment of chronic obstructive pulmonary disease. Its potential role as a treatment for asthma is unclear.
Aim: We report the results from seven double-blind, parallel group, phase II or III studies designed to compare roflumilast with two anti-inflammatory treatments, beclomethasone dipropionate (BDP) and montelukast, in patients with asthma.
Methods: The studies of 6–12 week duration were conducted at 309 sites in Europe, North America, South Africa and Australia from 1998 to 2005. Data from 3802 patients, aged 12–70 years who received either roflumilast 100 μg, 250 μg or 500 μg once daily, BDP 400 μg or 500 μg twice daily, or 10 mg montelukast once daily was analyzed. Primary endpoints were mean change and time averaged excess area under the curve in forced expiratory volume in one second (FEV_1) over the duration of the study. Secondary endpoints included change in forced vital capacity and peak expiratory flow, asthma symptoms and the concomitant use of rescue medication.
Results: Roflumilast was non-inferior to BDP and montelukast and consistently increased FEV_1. Use of rescue medication and all asthma symptom scores decreased significantly with all treatments, but no statistically significant between-group differences were observed. Secondary lung function endpoints generally supported the conclusions of the primary outcome measure.
Conclusions: Roflumilast improves FEV_1 and asthma symptoms in patients with mild to moderate asthma, and is non-inferior compared with both BDP and montelukast. It deserves further study as a potentially effective anti-inflammatory treatment for asthma.

1. Introduction

For optimum asthma symptom control, guidelines recommend the step-wise increase in dose of inhaled corticosteroid (ICS) and/or the addition of other controller medications in patients who fail to achieve target levels of control at lower steps [1]. At treatment Step 2, although regular treatment with low-dose ICS is the preferred treatment, monotherapy with leukotriene modifiers such as montelukast is an alternative option but is less effective both for symptom control and exacerbation prevention [1,2]. The preferred add-on treatment to ICS is a long-acting beta-agonist (LABA), but leukotriene modifiers such as montelukast and theophylline, though also recommended, are less effective [1–3] and their role as add-on treatment in more severe asthma (Steps 4 and 5) is not well studied [2,4]. Nor is there robust evidence of the benefit that may result when these three add-on treatments are combined [1]. Since asthma is a heterogeneous disease it is not surprising that anti-inflammatory treatments with different mechanisms of action are beneficial both as monotherapy and when combined, and the search for additional options has resulted in the development of a variety of classes of treatment, including phosphodiesterase-4

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inhibitors [4,5], monoclonal antibodies, IgE, and other inflammatory targets [5].

As described in companion papers in this edition of the journal (Meltzer et al., Placebo-controlled studies and Bardin et al., Mechanism of Action studies), the pharmacology and mechanism of action of the oral phosphodiesterase-4 inhibitor roflumilast and its confirmed role in the management of COPD (it is approved in patients with severe COPD associated with chronic bronchitis and a history of exacerbations), support a potential role for it in the treatment of asthma [6,7]. The indication in severe chronic obstructive pulmonary disease (COPD) is as an add-on treatment for patients with symptoms of chronic bronchitis and a history of frequent exacerbations. Roflumilast improves lung function and reduces the frequency of exacerbations in such patients [8–10] presumably as a consequence of its anti-inflammatory properties [11].

This report provides the results of early studies of roflumilast in asthma (the roflumilast in asthma programme) including seven that compared roflumilast with the two established anti-inflammatory treatments, beclomethasone dipropionate (BDP) and montelukast. Two studies compared its efficacy with BDP and three studies compared roflumilast with montelukast. An additional two studies examined the optimal dose and time of dosing of roflumilast in patients with asthma. This report summarizes the results of these studies, and provides the basis for exploring further the role of roflumilast as a controller treatment for asthma.

2. Methods

2.1. Overview of asthma studies

A total of 3802 patients were randomized in seven double-blind, parallel group, phase II or III studies conducted at study sites in Europe, North America, South Africa and Australia from 1998 to 2005. Five studies were designed to investigate the non-inferiority of oral roflumilast given once-daily versus montelukast or BDP. Endpoints in each study included change in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF), asthma symptoms and the concomitant use of rescue medication. Patients also recorded their daily morning and evening PEF, use of rescue medication and night- and day-time symptoms of asthma in a diary throughout the studies (Table 1).

2.2. Patients

Patients aged 12–70 years with a history of asthma and a pre-bronchodilator FEV_1 between 50 and 85% of predicted at randomization were eligible for enrolment into the seven studies (Table 1). Exclusion criteria included: poorly controlled asthma or an asthma exacerbation occurring within four weeks of the baseline visit that required treatment with oral corticosteroids, hospitalization due to deteriorating asthma control, regular use of >8 puffs of rescue medication/day (>6 puffs/day in study FK1 008) and a diagnosis of COPD or other relevant lung disease (see Table S1 for pooled patient demographic and baseline characteristics including smoking history and prior ICS use).

2.3. Studies

During the single-blind run-in periods (which varied from 1 to 4 weeks duration), all asthma controller medications were withdrawn and patients received placebo. Eligible patients were then randomly allocated in the different studies to receive roflumilast 100 μg, 250 μg or 500 μg once daily, BDP 400 μg or 500 μg twice daily, or 10 mg montelukast once daily. The randomization scheme was 1:1 in four studies (FK1 008, M2 015, M2 017 and M2 026), 2:1 in study FK1 005, and 1:1:1 in studies FK1 006 and FK1 009. During double-blind treatment, patients were instructed to use a short-acting beta agonist (SABA) (usually salbutamol) as rescue medication. Rescue medication was withheld for four hours before spirometry performed at clinic visits. Visits took place in the morning.

2.3.1. Roflumilast phase II posology/dose-finding studies M2 015 (402 patients) and FK1 006 (693 patients)

Study M2 015 compared the efficacy, safety, tolerability and pharmacokinetics of 500 μg roflumilast administered either once-daily in the morning or evening, during a 6-week treatment period. Study FK1 006 was a roflumilast dose-range finding study; efficacy and safety were investigated and compared at three doses: once-daily 100 μg, 250 μg and 500 μg given in the morning over 12 weeks.

2.3.2. Roflumilast vs BDP studies FK1 005 (phase II; 232 patients) and FK1 009 (phase III; 499 patients)

These studies compared the efficacy of 500 μg roflumilast once-daily with 400 μg or 500 μg BDP twice daily during a 6- or 12-week treatment period, in order to establish the non-inferiority of roflumilast.

2.3.3. Roflumilast vs montelukast studies FK1 008 (phase III; 445 patients), M2 017 (phase IIIb; 958 patients) and M2 026 (phase IIIb; 573 patients)

These studies compared the efficacy of roflumilast 250 μg or 500 μg with 10 mg montelukast; treatments were taken once-daily either in the morning (roflumilast) or in the evening (montelukast). They were designed to determine whether roflumilast taken daily during a 12- or 24-week period was statistically non-inferior (at least equivalent) to 10 mg montelukast.

2.4. Endpoints

The primary endpoint in six of the seven studies was the mean change in FEV_1 during the treatment period. In study M2 017 the primary endpoint was time-averaged excess (TAE) area under the curve (AUC) of FEV_1 from treatment start to end. Common secondary endpoints across the seven studies included measurements of FEV_1, FVC and PEF, and diary measurements of morning and evening PEF, PEF diurnal variation, mean change from baseline in asthma symptom scores, number of symptom and rescue medication-free days, mean change from baseline for rescue medication intake, drop-outs due to lack of efficacy (LOE)/escape criteria and subjective effectiveness rating. These are summarized for each study in Table 1. Results from only selected secondary endpoints are presented in this report.

2.5. Key subgroup analysis

The mean change in FEV_1 in patients with/without ICS pre-treatment was investigated during the treatment period in study FK1 006.

2.6. Safety

Safety monitoring for all studies included adverse events, laboratory tests, physical examination findings, electrocardiograms and vital signs.