Roflumilast combined with montelukast versus montelukast alone as add-on treatment in patients with moderate-to-severe asthma

Eric D. Bateman, MD,[a] Udo-Michael Goehring, MD,[b] Frank Richard, MD,[c] and Henrik Watz, MD[d] *Cape Town, South Africa, Zurich, Switzerland, and Biberach and Grosshansdorf, Germany*

Background: Roflumilast, a selective phosphodiesterase 4 inhibitor, has been shown to provide modest improvements in lung function in patients with mild-to-moderate asthma, but its efficacy in patients with moderate-to-severe asthma has not been assessed. We hypothesized that this drug might provide benefit if combined with montelukast, a leukotriene receptor antagonist, in patients whose symptoms are uncontrolled by inhaled corticosteroids and long-acting β-agonists.

Objective: We sought to examine the efficacy, safety, and mode of action of the addition of roflumilast and montelukast versus montelukast alone in patients with moderate-to-severe asthma.

Methods: In a phase 2, randomized, double-blind, placebo-controlled, multiple-dose, 2-sequence, crossover study, 64 patients were randomized to receive 500 μg of roflumilast plus montelukast followed by placebo plus 10 mg of montelukast (sequence AB) or placebo plus 10 mg of montelukast followed by 500 μg of roflumilast plus 10 mg of montelukast (sequence BA). All patients had a diagnosis of bronchial asthma inadequately controlled by at least a medium-dose inhaled corticosteroid plus a long-acting β-agonist.

Results: The analysis of FEV_1 change from baseline to week 4 showed a statistically significant and clinically meaningful treatment difference of 100 mL for roflumilast plus montelukast versus placebo plus montelukast. Also, improvements in patient-reported outcomes and a reduction in urinary leukotriene E_4 levels were observed during roflumilast plus montelukast treatment compared with placebo plus montelukast treatment. Adverse events were consistent with the known safety profile of roflumilast.

Conclusion: The combination of roflumilast with montelukast compared with montelukast alone improved lung function and asthma control in patients with moderate-to-severe asthma and deserves further study for this indication. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Asthma, roflumilast, montelukast, phosphodiesterase 4 inhibitors*

The recent American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force on Severe Asthma has defined severe asthma as asthma requiring Global Initiative for Asthma step 4 or 5 treatment (high-dose inhaled corticosteroids [ICSs] and long-acting β-agonists [LABAs] or leukotriene modifier or theophylline) for the previous year to prevent it from becoming "uncontrolled" or that remains "uncontrolled despite this therapy."[1,2] Treatment options for severe asthma are limited and include omalizumab,[3] an anti-IgE antibody treatment indicated only in a select phenotype of patients with high serum IgE levels, oral corticosteroids, and, more recently, bronchial thermoplasty and tiotropium.[1-4] Although recommended, montelukast is not approved for patients with severe asthma in some countries, and there is little evidence from prospective trials supporting the efficacy of leukotriene modifiers and theophylline added to other controllers, such as a high-dose ICS and LABA at steps 4 and 5.[1,2,5]

Current research in asthma is focused on the development of treatments that target specific components of airway inflammation,[3] and results with anti–IL-4, anti–IL-5, and anti–IL-13 treatments are promising.[1,6,7] However, these treatments are likely to be suitable only for patients with well-defined endotypes of disease, and there might be a role for combining different classes of treatment, including those that are not restricted by phenotype. Recognized phenotypes in asthmatic patients based on sputum examination are eosinophilic (usually associated with T_H2-driven pathways), neutrophilic (or granulocytic), and paucicellular.[1,8] The Severe Asthma Research Program recognized patients with the mixed granulocytic phenotype as having more severe disease (lowest lung function, most symptoms, and

From [a]the Division of Pulmonology, Department of Medicine, University of Cape Town; [b]Takeda Pharmaceuticals International GmbH, Zurich; [c]Boehringer Ingelheim Pharma GmbH & Co, Biberach; and [d]the Pulmonary Research Institute at Lung Clinic Grosshansdorf, Airway Research Centre North, Member of the German Center for Lung Research, Grosshansdorf.

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Corresponding author: Eric D. Bateman, MD, Division of Pulmonology, Department of Medicine, University of Cape Town, George Street, Mowbray 7700, Cape Town, South Africa. E-mail: Eric.Bateman@uct.ac.za.

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Abbreviations used
ACQ: Asthma Control Questionnaire
AE: Adverse event
ANCOVA: Analysis of covariance
ATS: American Thoracic Society
BMI: Body mass index
COPD: Chronic obstructive pulmonary disease
C-SSRS: Columbia Suicide Severity Rating Scale
ERS: European Respiratory Society
$FEF_{25-75\%}$: Forced expiratory flow between 25% and 75% of forced vital capacity
FENO: Fraction of exhaled nitric oxide
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
IVRS: Interactive voice response system
LABA: Long-acting β-agonist
LS: Least square
LTE_4: Leukotriene E_4
MAP: Multi Analyte Profile
PDE-4: Phosphodiesterase 4
PEF: Peak expiratory flow
SABA: Short-acting β-agonist
TEAE: Treatment-emergent adverse event

higher health care use) and greater corticosteroid refractoriness.[8] This heterogeneity provides the basis for combining treatments that target different mechanisms, including some that can also influence neutrophils.

The selective inhibitor of phosphodiesterase 4 (PDE-4), roflumilast, is currently approved for use in patients with chronic obstructive pulmonary disease (COPD) in several countries. Inhibition of PDEs leads to an increase in intracellular cAMP levels and suppression of inflammatory responses.[9,10] In patients with mild asthma, roflumilast has been shown to inhibit asthmatic reactions to antigens,[11,12] reduce sputum eosinophil and neutrophil counts,[12,13] and be effective in patients with exercise-induced asthma.[14] Efficacy has also been demonstrated in patients with mild-to-moderate asthma.[15] In patients with COPD, it is prescribed as an oral once-daily maintenance treatment (500 μg) and indicated as add-on treatment (to bronchodilator treatment with or without ICSs) for patients with severe and very severe COPD associated with chronic bronchitis and a history of frequent exacerbations.[16-18]

Using a crossover study design, we set out to examine the potential of combining roflumilast and montelukast, anti-inflammatory treatments with different modes of action, compared with montelukast and a placebo in patients with uncontrolled asthma receiving at least a moderate dose of ICS plus LABA. In addition to assessing the safety and clinical end points of pulmonary function, symptoms, and asthma control, we explored selected serum and urinary biomarkers to cast light on the potential mode of action of these treatments.

METHODS

Patients

We enrolled patients aged 18 or more years who had asthma of at least 6 months' duration that was inadequately controlled (Asthma Control Questionnaire [ACQ-7] score ≥1.5) despite at least a medium-dose ICS at a stable dose (fluticasone propionate, ≥250 μg/d or equivalent) plus LABA therapy during the 4 weeks before screening. Additional requirements were a prebronchodilator FEV_1 of greater than 55% but 85% or less of predicted value at the screening and at least a 12% and 200-mL improvement in FEV_1 after inhalation of a short-acting β-agonist (SABA) recorded in the previous 12 months or at screening. Patients were excluded if they were current smokers or had a smoking history of 10 or more pack years or had experienced a severe asthma exacerbation or a lower respiratory tract infection within 4 weeks of the baseline visit. A full list of inclusion/exclusion criteria and prohibited concomitant medications is provided in Appendices E1 and E2 in this article's Online Repository at www.jacionline.org.

During the study, salbutamol (100 μg per puff) administered through a pressurized metered-dose inhaler was used as as-needed reliever medication. All patients continued to receive their current maintenance ICS and LABA therapy at a constant dose throughout the study. Other controller therapies were not permitted.

Study design

This was a phase 2, randomized, placebo-controlled, multiple-dose, 2-sequence crossover study, with two 4-week treatment periods separated by a 4-week washout period (Fig 1). A 4-week crossover design was chosen primarily to reduce between-patient variability and minimize the required number of patients. The treatment duration was limited to 4 weeks to reduce potential influences of season and baseline health, and based on previous studies with these drugs, this was long enough to demonstrate potential efficacy. The study was conducted between January and October 2013 at 15 sites in Germany, Hungary, and South Africa. During the double-blind treatment phase, patients were randomly assigned to 1 of 2 treatment sequences. The method of randomization is described in the Methods section in this article's Online Repository at www.jacionline.org.

Study end points

The primary efficacy end point was change in prebronchodilator FEV_1 from baseline and the end of the washout period to week 4 (the end of each treatment period) measured in the clinic by using the same spirometer for each patient throughout the study according to ATS/ERS consensus guidelines for pulmonary function testing.[19] Secondary efficacy end points were change in prebronchodilator forced vital capacity (FVC), forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$), and peak expiratory flow (PEF) at the same time points: morning PEF was obtained from home measurements, and daytime and nighttime asthma symptoms were recorded by using an ePEF meter.[19] Asthma control was measured by using the ACQ-7 (see the Methods section in this article's Online Repository).[20] Exploratory end points included total and differential WBC counts, a panel of 46 inflammatory mediators in serum measured by using the Human Inflammation Multi-Analyte Profile (MAP) detection panel (Myriad RBM kit; Rules-Based Medicine, Austin, Tex), symptoms, as-needed SABA use, ACQ-7 scores, and urinary leukotriene E_4 (LTE_4) levels.[21,22] In a *post hoc* responder analysis the number of patients who achieved an ACQ-7 score decrease of 0.5 or greater was also summarized. Additional exploratory end points included asthma exacerbations and dropouts caused by adverse events (AEs).

In 14 (21.9%) patients differential cell counts and inflammatory biomarkers in induced sputum, fraction of exhaled nitric oxide (FENO), and FENO/LTE_4 ratio were measured by using the recommended methods.[19] The analysis of inflammatory mediators in dithiothreitol-treated sputum supernatants was performed with the Human Inflammation MAP detection panel (Myriad RBM kit; Rules-Based Medicine; see the Methods section in this article's Online Repository).[22]

Safety

Safety monitoring included AEs, laboratory tests, measurement of body mass index (BMI) and vital signs, and electrocardiography. Safety assessment continued for 30 days after the active treatment period. The protocol was approved by relevant health authorities and local institutional review boards. The study was conducted according to Good Clinical Practices Guidelines and the Declaration of Helsinki. All patients provided written informed consent for study participation.