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CLINICAL TRIAL PAPER

A 24-week comparison of low-dose ciclesonide and fluticasone propionate in mild to moderate asthma

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Asthma control;
Ciclesonide;
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Low-dose inhaled corticosteroid

Summary
Objective: To compare the efficacy of ciclesonide (80 μg/day) with fluticasone propionate (200 μg/day) in mild to moderate persistent asthma.
Methods: Patients aged 12–75 years and previously treated with low doses of inhaled corticosteroid (fluticasone propionate 250 μg/day or equivalent) entered a 2–4 week run-in period during which only rescue medication was permitted. For inclusion into the double-blind, 24-week treatment period, patients had to show a forced expiratory volume in 1s (FEV_1) of 61–90% predicted and a decrease in FEV_1 during run-in of ≥10%. Patients ($n = 480$) were randomized to ciclesonide 80 μg (ex-actuator) once daily in the evening or fluticasone propionate 100 μg (ex-valve) twice daily. The primary efficacy variable was the change from baseline in FEV_1. Secondary efficacy variables included asthma control and asthma-specific quality of life.
Results: Both treatments significantly increased FEV_1 and other lung function variables from baseline ($p < 0.0001$, both groups, all variables). The least squares mean increases in FEV_1 were 0.46L (ciclesonide) and 0.52L (fluticasone propionate); non-inferiority of ciclesonide to fluticasone propionate was demonstrated ($p = 0.0002$, per-protocol analysis). Five patients in each group experienced asthma exacerbations. Improvements in the percent of days with asthma control (days with no asthma symptoms and no use of rescue medication) and asthma-specific quality of life were comparable between treatments.

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Conclusions: The study confirmed similar efficacy of ciclesonide 80 μg once daily and fluticasone propionate 100 μg twice daily in mild to moderate persistent asthma. The low dose of ciclesonide was efficacious during long-term treatment.

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Introduction

Bronchial asthma is one of the most common chronic diseases worldwide and accounts for 1% of the total annual global burden of disease.[1] There is still no cure for asthma, but pharmacological therapy can either provide acute symptom relief or tackle the underlying inflammatory processes to achieve clinical control of asthma on a long-term basis. Inhaled corticosteroids are currently the most effective anti-inflammatory agents in asthma therapy and are recommended by national and international guidelines as first-line treatment for persistent asthma, either alone or in combination with long-acting beta-agonists.[2,3]

Ciclesonide is a glucocorticosteroid-ester prodrug, currently approved for the treatment of persistent asthma in more than 50 countries. It is formulated as a solution for inhalation by means of a pressurized metered-dose inhaler (MDI) with hydrofluoroalkane (HFA) 134a as a propellant. Efficacy of ciclesonide has been demonstrated in numerous placebo-controlled and comparative studies in adults and children with asthma of all severities.[4,5] In Europe, the recommended starting dose of ciclesonide in adolescents and adults is 160 μg once daily. A lower dose of ciclesonide, 80 μg once daily, significantly improved lung function variables compared with placebo in patients with mild to moderate persistent asthma in two 12-week studies.[6,7] In addition, ciclesonide 80 μg once daily attenuated the early and late asthmatic responses after allergen challenge and significantly improved exercise-induced bronchoconstriction after one week of treatment.[8,9] A comparative 12-week study in patients with persistent asthma (≥12 years) showed similar asthma control of two doses of ciclesonide, 80 μg and 160 μg (ex-actuator) once daily, and fluticasone propionate 100 μg (ex-valve) twice daily.[10]

Many patients with persistent asthma require long-term anti-inflammatory treatment for the prevention of asthma symptoms. To minimize the risk of side effects, the lowest effective dose of an inhaled corticosteroid should be used for maintenance treatment. The main objective of the present study was to confirm the long-term efficacy of ciclesonide 80 μg (ex-actuator) once daily over 24 weeks in patients with mild to moderate asthma. For this purpose, ciclesonide was compared with fluticasone propionate 100 μg (ex-valve) twice daily.

Methods

Patients

Female and male patients aged 12—75 years with a history of persistent bronchial asthma[11] for at least 6 months, but otherwise in good health were enrolled. Patients were eligible to enter a 2—4 week run-in period prior to randomization (baseline) if they had received inhaled corticosteroids (fluticasone propionate 250 μg/day or equivalent) at a constant dose during the last 4 weeks prior to the run-in period and if they exhibited a forced expiratory volume in 1s (FEV_1) between 80% and 105% predicted. Patients were excluded from the study if they had: other relevant lung diseases, e.g., chronic obstructive pulmonary disease, a severe concomitant disease, a condition that precluded the use of inhaled corticosteroids, or clinically relevant abnormal laboratory values. Female patients were excluded if they were pregnant, breastfeeding, or were not using reliable contraceptive methods. Current smokers and ex-smokers with ≥10 pack-years, patients starting immunotherapy, and patients with known or suspected hypersensitivity to inhaled corticosteroids or excipients of the metered-dose inhaler were also excluded. Systemic glucocorticosteroids were not to be used during the last 4 weeks or more than twice during the last 6 months prior to the run-in period.

For inclusion into the treatment period at baseline, patients had to have a FEV_1 between 61% and 90% predicted, a decrease in FEV_1 of ≥10% compared to the start of the run-in period, and reversible bronchial obstruction ($\Delta FEV_1 \geq 12\%$ predicted or ≥0.20L) after inhalation of 200—400 μg salbutamol. Patients were not to be randomized to treatment if they had a daytime asthma symptom score of ≥3 (5-point scale: 0—4) on more than 3 days or nighttime asthma symptoms on more than 2 nights during the last 7 days prior to randomization.

Study design

This was an international, multicentre, randomized, double-blind, double-dummy, 2-arm, parallel-group study with a 2—4 week run-in period (up to 4 visits) and a 24-week double-blind treatment period (6 visits). During the run-in period, patients received only rescue medication (inhaled salbutamol, 100 μg/puff) according to need. Patients who met the criteria for entering the treatment period were randomly assigned in a 1:1 ratio to receive ciclesonide 80 μg (ex-actuator) once daily in the evening or fluticasone propionate 100 μg (ex-valve) twice daily in the morning and evening (200 μg/day, equivalent to an ex-actuator dose of 176 μg/day). Study medications were administered via HFA-MDI. No spacer was used, but inhalation technique was reviewed at each visit during the treatment period. No other anti-asthma drugs, with the exception of rescue medication, were permitted during the treatment period.

Randomization was based on a computer-generated list (Program RANDOM).[12] The study was conducted at 48 centres in Austria, Canada, Germany, Poland, and South Africa in accordance with the principles of the revised Declaration of Helsinki (Somerset West, 1996) and the International Conference on Harmonization Topic E6: Guideline for Good