Short-Term Lower Leg Growth in 5- to 11-Year-Old Asthmatic Children Using Beclomethasone Dipropionate Inhalers With Chlorofluorocarbon or Hydrofluoroalkane Propellants: A 9-Week, Open-Label, Randomized, Crossover, Noninferiority Study

Ole D. Wolthers, MD[1]; and Ewan G. Walters, MBChB[2]

[1]*Children's Clinic Randers, Randers, Denmark; and* [2]*Teva UK Limited, Castleford, United Kingdom*

ABSTRACT

Background: Beclomethasone dipropionate–hydrofluoroalkane (BDP-HFA) is a non–chlorofluorocarbon (CFC)-propelled metered dose inhaler. Data is needed to support the registration of BDP-HFA in pediatric populations for countries in the European Union.

Objective: The aim of the study was to assess short-term lower leg growth in children with asthma during treatment with BDP-HFA 100 μg BID compared with BDP-CFC 200 μg BID.

Methods: Children with asthma were included in this open-label, randomized, crossover study with 2-week run-in, active treatment, and washout periods. Lower leg length was measured every second week. As a secondary outcome parameter, 24-hour urine was collected for assessment of free cortisol. Interventions were inhaled BDP-HFA 100 μg BID with AeroChamber Plus spacer and BDP-CFC 200 μg BID with Volumatic spacer.

Results: In 63 patients with asthma aged 5 to 11 years, BDP-HFA 100 μg BID was noninferior to BDP-CFC 200 μg BID, as the lower margin of CI (−0.03 to 0.10 mm/wk) of the estimated difference (0.03 mm/wk) was greater than the prespecified lower limit for noninferiority of −0.12 mm/wk. Mean (SD) lower leg growth rate during run-in, BDP-HFA 100 μg BID, and BDP-CFC 200 μg BID was 0.36 (0.17), 0.27 (0.21), and 0.23 (0.18) mm/wk, respectively (BDP-HFA estimate of difference, −0.09 [95% CI, −0.16 to −0.03 mm/wk; $P < 0.01$]; BDP-CFC estimate of difference, −0.13 [95% CI, −0.19 to −0.06 mm/wk; $P < 0.001$]). No statistically significant differences were seen in urinary free cortisol assessments. Eight and 6 mild to moderate adverse events in 10 children were reported during treatment with BDP-HFA and BDP-CFC, respectively. One event in each group was judged to be probably related to the study medication; no others were judged to be related.

Conclusions: No statistically significant differences were found in lower leg growth between BDP-HFA 100 μg BID with AeroChamber Plus spacer and BDP-CFC 200 μg BID with Volumatic spacer during 2-week treatment. Evidence of differences in systemic activity between the treatments was not found. EudraCT registration: 2007-007455-14. (*Clin Ther.* 2011;33:1069–1076)

Key words: adrenal function, asthma, beclomethasone dipropionate, corticosteroids, growth, hydrofluoroalkane-134a, lower leg growth, knemometry, steroids.

INTRODUCTION

Beclomethasone dipropionate (BPD) is a topically active synthetic corticosteroid widely used in the treatment of asthma in children.[1] As with other inhaled corticosteroids, during the past decade or so increasing focus has been placed on the risk of systemic activity of the drug and suppressive effects on growth and hypothalamic-pituitary-adrenal function.[1,2] For many years BDP was delivered via the Volumatic volume spacer (Allen & Hanburys, Stockley Park, United Kingdom) from a pressurized metered dose inhaler (pMDI) containing BDP and chlorofluorocarbon (CFC) as propellant.[3] During the past 15 years, however, pMDIs containing CFC have been phased out owing to the deleterious effects of CFC on the ozone layer. The alternative propellant hydrofluroroalkane-134a (HFA)

Accepted for publication June 20, 2011.
doi:10.1016/j.clinthera.2011.06.015
0149-2918/$ - see front matter

does not affect the ozone layer.[4] BDP-HFA* is an inhalation aerosol containing BDP as active principle and hydrofluoroalkane (HFA-134a; norflurane; 1,1,1,2-tetrafluoroethane) as propellant.[5] BDP-HFA was launched in 1998 in the United Kingdom for the prophylactic management of mild, moderate, or severe asthma. It is delivered via a pMDI with an AeroChamber Plus volume spacer (Trudell Medical International, London, Ontario, Canada). Because the particle size of BDP-HFA is considerably smaller than that of the CFC formulation† (mass median aerodynamic diameter [MMAD] of 1.1 μm [BPD-HFA] vs 3.4 μm [BPD-CFC]), concern has been raised that an increased pulmonary deposition rate may be associated with an increase in systemic bioavailability and, hence, effects on growth and cortisol secretion.[6] In accordance with this, to support the registration for BDP-HFC in children with asthma, comparative data on short-term growth in children with asthma treated with BDP-HFA 100 μg BID with AeroChamber Plus spacer and BDP-CFC 200 μg BID with Volumatic spacer were requested. As a secondary aim, hypothalamic-pituitary-adrenal function was also assessed in the present study.

PATIENTS AND METHODS

The study was powered to demonstrate noninferiority between lower leg growth rates during treatment with BDP-CFC 200 μg BID with Volumatic spacer and BDP-HFA 100 μg BID with AeroChamber Plus spacer.[7] A power calculation based on the SD on the difference in lower leg growth rates from previous knemometry studies (0.30 mm/wk) showed that to be able to demonstrate with 80% power that the lower end of the 1-sided 97.5% CI for the difference in lower leg growth rates between BDP-CFC 200 μg BID and BDP-HFA 100 μg BID would be above −0.12 mm/wk, 52 subjects had to complete the study.[6,7] Because the withdrawal rate in short-term knemometry studies may be 20% to 40%, a total of 64 children were enrolled.[8]

Inclusion criteria included male and female prepubertal (Tanner stage 1) patients aged 5 to 11 (inclusive) with a documented history and confirmed diagnosis of asthma[9]; normal growth development (height between the 3rd and 97th percentiles) according to Danish standard height growth charts; current use of either short-acting β2 agonist and/or low-dose (≤200 μg BID) inhaled corticosteroid; ability to correctly use a peak flow meter; demonstrated satisfactory technique in the use of pMDIs and spacer; willingness and ability to accurately complete patient diary cards with assistance from parents/guardian; capability of reading and understanding informed consent (assent for those younger than the legal contractual age of consent) and the patient information leaflet by each patient and both parents/guardian; and written informed consent by both parents/guardian with assent from each patient before any trial procedure was carried out.

Exclusion criteria included patients who had entered puberty; current or prior (ie, in the 4 weeks preceding visit 1) use of high-dose (>200 μg BID) inhaled corticosteroids; concomitant severe diseases or diseases that the investigator believed were contraindications to the use of bronchodilators or that could affect study outcome measures, including malignancies; chronic systemic or lung disease (ie, cystic fibrosis); inpatient hospitalization for acute therapy of asthma during the 3 months preceding visit 1; current or recent (within 3 months before visit 1) systemic (oral, parenteral, or depot) corticosteroid therapy or receipt of >3 short courses of systemic corticosteroid therapy in the preceding year; continuous use of long-acting β2 agonists (inhaled, oral, or otherwise) for asthma symptoms; asthma exacerbation or respiratory tract infection requiring antibiotic treatment during 6 weeks before visit 1; known or suspected hypersensitivity of any inhaled corticosteroid or any one of the excipients of the pMDIs; inability to perform lung function tests; a suspicion of being unlikely to be compliant, take medication as directed, complete the lung function testing procedures, or attend scheduled clinic visits; and participation in an investigational drug trial during 30 days preceding visit 1. In addition, peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1) needed to be >80% of expected values at the screening visit. A decrease in pulmonary function by ≥25% of the value was grounds for exclusion from the study.

The study was conducted in accordance with international guidelines issued by the European Commission in 1990 and the Declaration of Helsinki and approved by the local ethics committee.[10] Informed consent and assent, respectively, were obtained from all parents and children. International Conference on Harmonisation for Good Clinical Practice (ICH/GCP)

*Trademark: Qvar® (Teva UK Limited, Castleford, United Kingdom).

†Trademark: Beclazone® (Teva UK Limited, Castleford, United Kingdom); discontinued in 2010.