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Real-life comparison of beclometasone dipropionate as an extrafine- or larger-particle formulation for asthma

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Summary
Background: Beclometasone dipropionate is an inhaled corticosteroid (ICS) available in both extrafine and larger-particle hydrofluoroalkane formulations. Extrafine beclometasone has greater small airway distribution and inhalation technique tolerance than larger-particle beclometasone; therefore, its use may be associated with improved asthma outcomes at population levels. The study objective was to compare real-life effectiveness of extrafine and larger-particle beclometasone.
Methods: Retrospective matched cohort study including primary care patients with asthma (ages 12–60 and non-smokers 61–80 years) prescribed extrafine or larger-particle beclometasone by metered-dose inhaler. We studied patients receiving their first ICS (initiation population, $n = 11{,}289$) or switched from another ICS without dose change (switch population, $n = 19{,}065$). The extrafine and larger-particle beclometasone cohorts were matched in each population for demographic and database measures of asthma control during a baseline year; and endpoints assessed during 1 outcome year were adjusted for residual confounding factors.

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Results: The odds of no loss of asthma control (no asthma-related hospital attendance, consultation for lower respiratory tract infection, or oral corticosteroids) were significantly higher in the extrafine beclometasone cohorts of both initiation population (adjusted odds ratio [aOR] 1.12; 95% CI 1.02—1.23) and switch population (aOR 1.10; 95% CI 1.01—1.19). The odds of better adherence to ICS therapy were also significantly higher in both extrafine beclometasone cohorts (initiation population, aOR 1.64; 95% CI 1.52—1.75 and switch population, aOR 1.35; 95% CI 1.27—1.43).

Conclusions: These findings are consistent with the hypothesis that delivery of beclometasone in extrafine particle size produces real-life asthma treatment benefits.

Clinical trials no. NCT01400217.

Introduction

Beclometasone dipropionate is an inhaled corticosteroid (ICS) that is available in both extrafine and larger-particle formulations for administration by pressurised metered-dose inhaler containing hydrofluoroalkane (HFA) propellant. The mass median aerodynamic diameter particle size of extrafine beclometasone is 1.1 microns, and that of larger-particle beclometasone is 2.9 microns.[1] Both are formulated with beclometasone in solution, rather than in a suspension as for the now discontinued chlorofluorocarbon (CFC)-beclometasone.

Larger-particle beclometasone was deliberately engineered by addition of glycerol to the formulation to enable a "dose for dose" exchange when transferring from CFC to HFA inhaler propellant. In 6- and 12-week clinical trials, larger-particle beclometasone was equivalent in efficacy on a microgram-for-microgram basis to CFC-beclometasone with regard to asthma-related endpoints, with similar safety and tolerability profiles.[2]

By contrast, extrafine beclometasone is licensed to be prescribed at half the dose of the larger-particle beclometasone formulations.[1] Dose-ranging study results indicate that extrafine beclometasone has significantly greater effects on lung function than CFC-beclometasone on a microgram-for-microgram comparison.[3] The lung deposition of extrafine beclometasone is much greater than that of CFC-beclometasone (55—60% compared with 4—7% for CFC-beclometasone in healthy volunteers) and oropharyngeal deposition is lower (29—30% versus 90—94%).[4—6] When switched from CFC-beclometasone to extrafine beclometasone at half the dose, patients in short-term randomised controlled trials maintained similar degrees of asthma control, with comparable safety profile, while those in a 12-month pragmatic trial experienced significantly greater improvement in health-related quality of life and a significantly higher percentage of symptom-free days than patients maintained on CFC-beclometasone.[7—12]

Efficacy in randomised controlled trials, which study tightly defined populations outside the normal ecology of care, does not necessarily translate to effectiveness in a real-life clinical setting, where factors that can influence and interact with asthma-related outcomes include comorbidities, polypharmacy, smoking habits, poor inhaler technique, and suboptimal adherence.[13—16] Moreover, the benefits of an extrafine formulation are not easy to test in a controlled trial setting.[17] Smokers are usually excluded from these trials, as are patients with poor adherence and/or poor inhaler technique, and it would be unethical to maintain a control group of patients at increased risk of exacerbations without increasing their treatment. For these reasons, real-life research is needed to understand whether differences in ICS particle size and the associated difference in airway deposition have an impact on asthma outcomes in routine practice. An observational design can enable the study of large numbers of patients, potentially improving the generalisability of study results.[17]

The objective of this observational database study was to compare the real-life effectiveness of extrafine and larger-particle beclometasone for two populations of primary care patients with asthma: those who were prescribed ICS for the first time and those switched from another ICS with no change in CFC-beclometasone-equivalent dose. Our hypothesis was that the potential benefits of improved total and small airway deposition and lower oropharyngeal deposition with extrafine beclometasone would translate to better asthma-related outcomes (less unplanned healthcare use and fewer oral corticosteroid courses).

Methods

Data sources and patients

This retrospective matched cohort study used patient data contained in two computerised primary care databases in the UK. The General Practice Research Database (GPRD), now incorporated into the Clinical Practice Research Datalink (CPRD) is well-validated and used frequently for pharmaco-epidemiological research,[18—21] and included about 5 million active patients. The Optimum Patient Care Research Database (OPCRD) contains anonymised, research-quality data for 341,000 patients with respiratory disease at approximately 300 practices that subscribe to OPC for respiratory review services.[22]

Patients eligible for the study were 12—80 years old when they initiated ICS therapy for asthma (initiation population), or were switched with no change in CFC-beclometasone-equivalent dose to new ICS therapy (switch population), with a prescription for either extrafine beclometasone (Qvar, Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel) or larger-particle beclometasone (Clenil Modulite, Chiesi Ltd, Highfield, Cheadle, UK) by pressurised metered-dose inhaler. (Patients who received