Supplemental Materials

Asthma-related outcomes in patients initiating extrafine ciclesonide or fine-particle inhaled corticosteroids

Supplemental Methods

Study Design

The PHARMO Database Network (PHARMO Institute, The Netherlands)\(^{31}\) links drug dispensing records to hospital discharge records and other data sources using probabilistic linkage.\(^{32,33}\) PHARMO’s Outpatient Pharmacy Database comprises general practice and specialist prescribed healthcare products dispensed by the outpatient pharmacy. The dispensed records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Drugs dispensed are coded according to the World Health Organization Anatomical Therapeutic Chemical Classification System.\(^{34}\) Outpatient pharmacy data cover a catchment area representing 3.6 million residents. The Hospitalization Database comprises hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required; emergency department attendance is not captured. The records include information on discharge diagnoses, procedures, and hospital admission and discharge dates.

The study was conducted to standards suggested for observational studies, including an independent advisory group, use of an \textit{a priori} analysis plan, study registration with commitment to publish, and a well-maintained and monitored study database.\(^{35}\) The study was approved by the PHARMO compliance and governance board.\(^{36}\) The study protocol was informed by the suggestions of the independent advisory group comprising members of the Small Airways Study Group of the Respiratory Effectiveness Group\(^{37}\) and was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, study no. 6148).\(^{38}\) The analyses and the dissemination of the results were approved by the advisory group and were conducted in accordance with the Respiratory Effectiveness Group standards and the ENCePP Code of Conduct.\(^{39}\)

The study design is depicted in Supplementary Fig. 1.

Endpoints

Co-primary endpoints for this study were assessed during 1 year after initiation of inhaled corticosteroid (ICS) therapy and included (1) the rate of severe exacerbations, defined as asthma-related hospital admissions or prescriptions of acute oral corticosteroids (based on the American Thoracic Society/European Respiratory Society definition)\(^{40}\) minus emergency department attendance, not available in the database); (2) risk-domain asthma control, defined as the absence of severe exacerbations; and (3) overall asthma control, defined as achieving risk-domain asthma control plus using a mean daily dose of salbutamol \(\leq 200 \mu g\) (\(i.e., 1\) dose/day on average, designed to capture symptom control).

Secondary study endpoints included change in therapy during the outcome period (defined as an ICS dose increase of \(\geq 50\%\) or addition of new therapy including a leukotriene receptor antagonist [LTRA], theophylline, or long-acting \(\beta_2\)-agonist [LABA]); and (2) average daily dose of short-acting \(\beta_2\)-agonists (SABA) defined as (the count of inhalers \(\times\) doses in pack/365) \(\times 1\mu g\) strength. Additional endpoints were the controller-to-total medication ratio in the year after the initiation date, estimated as the number of controller units/(number of controller units + number of reliever units), where controllers included ICS and LTRA. Two exploratory endpoints were (1) outcome prevalence of oral candidiasis, based on topical oral antifungal prescriptions and (2) outcome hospitalization rate (defined as number of hospital admissions for asthma or any lower respiratory reason).

The doses of ciclesonide and fluticasone are reported as actual doses; the beclomethasone doses were halved and are thus reported as fluticasone-equivalents, as per recommendations regarding corticosteroid equivalence.\(^{40-43}\)

Patients and Matching

Eligibility criteria were defined to identify patients in the database prescribed ICS for the first time for asthma and to minimize potential confounding factors. Patients eligible for this study were aged 12-60 years, had \(\geq 1\) full year of baseline and \(\geq 1\) full year of outcome data before and after first prescription of ICS on the initiation date, and had received two or more prescriptions for asthma at any time in their records in addition to the first ICS prescription, including at least one more ICS prescription during the outcome period (but no ICS before the initiation date). We excluded patients with any other recorded chronic respiratory disease at any time and, to minimize the potential for including patients with chronic obstructive pulmonary disease, we excluded patients \(>60\) years old and those prescribed long-acting muscarinic antagonists. Additional exclusion criteria were (1) maintenance oral corticosteroid therapy during the baseline period, (2) multiple ICS at the initiation

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date, and (3) theophylline or LTRA prescribed at the initiation date.

Patients were matched using 1:1 exact-matching methods.\textsuperscript{E14} Matching was conducted before the analysis of outcomes and thus was blinded to outcomes. We undertook 1:1 matching rather than propensity score matching because the latter may allow factors that interact with treatment response not to be matched for individual patients. This is because propensity score matching is a technique that matches patients using a score (the propensity score) defined as “the conditional probability of receiving the exposure of interest given measured covariates.”\textsuperscript{E15,E16} As a consequence, two patients matched using a propensity score can actually differ regarding individual variables used to build the score; for instance, this would occur if there is a difference in one direction (i.e., increasing exposure’s probability for one of the patients) for a given variable and in the opposite direction (decreasing exposure’s probability for this same patient) for another variable.

Our matching criteria were chosen before the study analysis based on differences in key baseline demographic and clinical characteristics of unmatched patients, expert clinical advice, and previous research experience and included the following: sex, age (±3 years for patients aged 12-18 years and ±5 years for those aged >18-60 years), absence of asthma-related hospital admissions and prescriptions for acute courses of oral corticosteroids (i.e., baseline risk-domain asthma control: controlled/not controlled), baseline LABA prescription (yes/no), baseline SABA daily dose (categorized as 0, 1-100, 101-200, and >200 µg/day), baseline LTRA prescription (yes/no), baseline prescription of antifungals to treat oral candidiasis (yes/no), and year of ICS therapy initiation (exact year). Patients were matched sequentially on each of the selected matching criteria; patients who did not match were excluded. At the end of the matching process, bespoke software was used to randomly select final matched pairs by eliminating double matches.

**Potential Confounding Factors Considered**

The rate ratios and odds ratios, with 95% confidence intervals, of matched patients for the endpoints were adjusted for appropriate non-collinear baseline confounders (Pearson and Spearman correlation coefficients, $\rho>0.30$) and for those variables predictive of the outcomes in a full multivariable model ($P \leq 0.05$).

Drawing on variables within the dataset:

1) Potential confounders examined at (or closest to) the ICS initiation date:
   - Age
   - Sex
2) Potential confounders examined in the year before the ICS initiation date:
   - Evidence of comorbidities, based on prescriptions for same (diagnoses also used, when available):
     - Rhinitis (prescriptions of nasal corticosteroid preparations)
     - Eczema (prescriptions for topical corticosteroid treatment)
     - Gastroesophageal reflux disease (prescriptions for proton pump inhibitors)
     - Cardiac disease (prescriptions for cardiac drugs or for hypertension)
     - Severe exacerbations
     - Risk-domain asthma control
     - Overall asthma control
     - Number of asthma-related or possibly respiratory-related hospitalizations
     - Other medications, number of prescriptions for the following:
       - Acetaminophen
       - Nonsteroidal anti-inflammatory drugs
       - β-blocker prescriptions
       - Theophylline
       - Statins
       - Tricyclics
     - Number of SABA prescriptions
     - ICS dose prescribed at initiation date
     - Controller-to-total medication ratio
     - Oral candidiasis

**References**


E9. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA,


