Original Article

Asthma–Related Outcomes in Patients Initiating Extrafine Ciclesonide or Fine–Particle Inhaled Corticosteroids

Dirkje S. Postma,[1] Richard Dekhuijzen,[2] Thys van der Molen,[1] Richard J. Martin,[3] Wim van Aalderen,[4] Nicolas Roche,[5] Theresa W. Guilbert,[6] Elliot Israel,[7] Daniela van Eickels,[8] Javaria Mona Khalid,[9] Ron M.C. Herings,[10] Jetty A. Overbeek,[10] Cristiana Miglio,[11] Victoria Thomas,[11] Catherine Hutton,[11] Elizabeth V. Hillyer,[11] David B. Price[11,12]*

[1]University of Groningen, Department of Pulmonology, University Medical Center Groningen, Groningen, The Netherlands
[2]Radboud University Medical Center, Nijmegen, The Netherlands
[3]Department of Medicine, National Jewish Health, and University of Colorado Denver, Denver, CO, USA
[4]Emma's Children Hospital AMC, Amsterdam, The Netherlands
[5]University Paris Descartes (EA2511), Cochin Hospital Group (AP-HP), Paris, France
[6]Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, USA
[7]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[8]Takeda Pharmaceuticals International GmbH, Zurich, Switzerland
[9]Takeda Development Centre Europe Ltd, London, UK
[10]PHARMO Institute for Drug Outcomes Research, The Netherlands
[11]Research in Real Life, Cambridge, UK
[12]Academic Primary Care, University of Aberdeen, Aberdeen, UK

Purpose: Extrafine-particle inhaled corticosteroids (ICS) have greater small airway deposition than standard fine-particle ICS. We sought to compare asthma-related outcomes after patients initiated extrafine-particle ciclesonide or fine-particle ICS (fluticasone propionate or non-extrafine beclomethasone). **Methods:** This historical, matched cohort study included patients aged 12-60 years prescribed their first ICS as ciclesonide or fine-particle ICS. The 2 cohorts were matched 1:1 for key demographic and clinical characteristics over the baseline year. Co-primary endpoints were 1-year severe exacerbation rates, risk-domain asthma control, and overall asthma control; secondary endpoints included therapy change. **Results:** Each cohort included 1,244 patients (median age 45 years; 65% women). Patients in the ciclesonide cohort were comparable to those in the fine-particle ICS cohort apart from higher baseline prevalence of hospitalization, gastroesophageal reflux disease, and rhinitis. Median (interquartile range) prescribed doses of ciclesonide and fine-particle ICS were 160 (160-160) µg/day and 500 (250-500) µg/day, respectively (*P*<0.001). During the outcome year, patients prescribed ciclesonide experienced lower severe exacerbation rates (adjusted rate ratio [95% CI], 0.69 [0.53-0.89]), and higher odds of risk-domain asthma control (adjusted odds ratio [95% CI], 1.62 [1.27-2.06]) and of overall asthma control (2.08 [1.68-2.57]) than those prescribed fine-particle ICS. The odds of therapy change were 0.70 (0.59-0.83) with ciclesonide. **Conclusions:** In this matched cohort analysis, we observed that initiation of ICS with ciclesonide was associated with better 1-year asthma outcomes and fewer changes to therapy, despite data suggesting more difficult-to-control asthma. The median prescribed dose of ciclesonide was one-third that of fine-particle ICS.

Key Words: Anti-asthmatic agents; comparative effectiveness research; disease exacerbation; small airway

INTRODUCTION

Asthma management guidelines recommend anti-inflammatory controller therapy to attenuate chronic airway inflammation in persistent asthma.[1-3] Inhaled corticosteroids (ICSs) are available inpressurized metered dose inhalers (pMDI) using a hydrofluoroalkane propellant as both fine-particle formulations with a particle mass median aerodynamic diameter (MMAD) of 2-4 μm and as aerosols of extrafine particles with an MMAD-1 μm.[4-6]

Ciclesonide is an extrafine-particle ICS (MMAD 1.0 μm) that shows both high lung deposition and peripheral lung distribution in healthy volunteers and patients with asthma.[7,8] Results of small studies in patients with mild-to-moderate asthma indicate that ciclesonide improves inflammation and patency of small airways[9] and, compared to fluticasone (MMAD 2.4-2.6 μm), provides greater improvement in small airway function, inflammation, and hyperresponsiveness to small-particle aerosolized adenosine monophosphate (MMAD 1.04 μm).[10,11] As small airways dysfunction may be involved in unstable asthma,[4,12-14] these findings raise the question whether there are differences ineffectiveness between extrafine- and fine-particle ICSs.

In clinical trials to date, ciclesonide showed similar efficacy as compared with fine-particle ICSs, such as fluticasone and budesonide (MMAD ~3 μm) at similar nominal doses for patients with persistent asthma.[10,15,16] However, these trials were generally 8-12 weeks in duration and focused on short-term improvement of lung function outcomes, thus they were unable to assess longer term fluctuations in asthma control and events, such as exacerbations. Moreover, smokers and patients with unstable asthma, who may both have more prominent small airways disease,[4,17] were typically excluded, as were patients with poor inhaler techniques, who might also benefit from extrafine-particle ICSs.[18] Thus, the question remains whether ICS particle size plays a role in long-term effectiveness of ICS therapy.

Non-interventional observational studies using high-quality databases can capture prescribing and medical record information to assess long-term outcomes for patients with asthma often excluded from clinical trials but commonly seen by clinicians, such as smokers, patients with poor inhaler techniques, patients at high risk of exacerbation, and those with comorbidities.[14,17,19,20] Previous database studies in the UK and USA have found in matched cohort analyses that the prescription of extrafine-particle beclomethasone was associated with equal, or better, asthma-related outcomes over a 1-year period, at significantly lower prescribed ICS doses, than standard fine-particle

fluticasone.[21,22] The aim of the current historical cohort study was to compare 1-year asthma-related outcomes between extrafine particle ciclesonide and 2 standard fine-particle ICS, fluticasone and non-extrafine beclomethasone, for patients in the Netherlands prescribed their first ICS.

MATERIALS AND METHODS

Data source

This was a historical, matched cohort effectiveness study of patients registered from September 2005 through December 2012 in the PHARMO Database Network (PHARMO Institute, Utrecht, The Netherlands), which links outpatient pharmacy and hospital discharge records for a catchment area representing 3.6 million residents (additional detail is provided in the Online Supplement).[23-25] The study was conducted to standards suggested for observational research, including an independent advisory group, use of an *a priori* analysis plan, and study registration.[26-28]

Patients and study design

Patients eligible for this study were aged 12-60 years, had ≥1 full year of baseline and ≥1 full year of outcome data before and after their first recorded prescription of ICS (*initiation date*), and had received 2 or more prescriptions for asthma at any time in their records in addition to the first ICS prescription, including at least 1 more ICS prescription during outcome (but no ICS during the baseline year); therefore, all patients included received at least 2 ICS prescriptions. We excluded patients >60 years old, those with any other recorded chronic respiratory disease, and those prescribed long-acting muscarinic antagonists or maintenance oral corticosteroid therapy during the baseline year.

At the initiation date, patients received a first prescription of ICS delivered using a pMDI as the extrafine-particle ICS ciclesonide (Alvesco®, Takeda Pharmaceuticals International GmbH, Zurich, Switzerland) or a pMDI fine-particle ICS, either fluticasone propionate (Flixotide®, GlaxoSmithKline, Brentford, Middlesex, UK) or non-extrafine beclomethasone dipropionate (Supplementary Fig. 1).

Study endpoints

Co-primary endpoints were assessed during 1 outcome year after initiation of ICS therapy and included (1) the rate of severe exacerbations, defined as asthma-related hospital admission or acute oral corticosteroid prescription (based on the American Thoracic Society/European Respiratory Society definition[29] excluding 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 mean daily dose of albuterol of ≤200 μg. Secondary endpoints

included the change in therapy and mean daily dose of short-acting β2-agonists (SABA) during the outcome period (additional detail in the Online Supplement).

Statistical analysis

Analyses were carried out using IBM SPSS Statistics version 22, Microsoft Office EXCEL 2007, and SAS version 9.3. Statistical significance was defined as $P<0.05$. Chi-square or Mann Whitney U-tests (unmatched data) and conditional logistic regression (matched data) were used to compare treatment cohorts at baseline.

Patients in the 2 cohorts were matched using 1:1 exact-matching methods,[30] described in the Online Supplement. Matching variables were sex, age, baseline risk-domain asthma control, prescribed long-acting β2-agonist, SABA daily dose, prescribed leukotriene receptor antagonist, prescribed antifungal medication for oral candidiasis, and year of ICS therapy initiation.

A conditional Poisson regression model was used to compare the rates of severe exacerbations and hospitalizations for matched patients. Conditional binary logistic regression was used to compare the odds of achieving asthma control, being prescribed higher doses of SABA, and changing therapy. Rate ratios and odds ratios, with 95% confidence intervals, were adjusted for appropriate non-collinear confounders.

RESULTS

Patients

There were 4,064 eligible patients identified in the database during the study period; 1,382 (34%) were prescribed extrafine-particle ciclesonide, and 2,682 (66%) fine-particle ICS. Applying the matching criteria led to 1,244 patients being selected in each treatment cohort (Supplementary Fig. 2).

After matching, baseline asthma control measures, SABA daily dose, and prior maintenance asthma therapy were comparable between the cohorts (Table 1). Asthma-related hospital admissions during the baseline year, while generally infrequent, were significantly more prevalent in the ciclesonide cohort (Table 1); significantly more patients who received ciclesonide had evidence of rhinitis (43% vs 38%; $P=0.004$) and were prescribed proton pump inhibitors (41% vs 34%; $P<0.001$) than those who received fine-particle ICS.

At the initiation date, ciclesonide was prescribed at significantly lower doses than fine-particle ICS (median [interquartile range] 160 [160-160] vs 500 [250-500] μg; $P<0.001$). The distribution of doses at initiation (Fig. 1) shows clear separation between ciclesonide (mostly 160 μg/day) and fine-particle ICS (mostly ≥500 μg/day, especially for fluticasone) (Supplementary Table 1).

Co-primary endpoints

During the outcome year, patients prescribed ciclesonide had

Table 1. Demographic and clinical characteristics of the matched patients

Characteristic	Treatment cohort	
	Ciclesonide n=1,244	Fine-particle ICS n=1,244
Female sex*	808 (65.0)	808 (65.0)
Age in years, median (IQR)	45 (34-53)	45 (35-53)[††]
Age in years, categorized*		
12-20	106 (8.5)	107 (8.6)
21-30	129 (10.4)	133 (10.7)
31-40	228 (18.3)	231 (18.6)
41-50	355 (28.5)	357 (28.7)
51-60	426 (34.2)	416 (33.4)
Comorbidities and co-medications		
Evidence of rhinitis[†]	539 (43.3)	469 (37.7)**
Evidence of GERD/GERD prophylaxis[‡]	504 (40.5)	420 (33.8)[††]
Evidence of oral candidiasis*,[§]	2 (0.2)	2 (0.2)
Year of ICS therapy initiation, median (IQR)*	2009 (2007-2010)	2009 (2007-2010)
Prior therapy		
SAMA	41 (3.3)	54 (4.3)
LABA*	8 (0.6)	8 (0.6)
LTRA*	3 (0.2)	3 (0.2)
Theophylline	1 (0.1)	0 (0)
Risk-domain asthma control*	1,127 (90.6)	1,127 (90.6)
Asthma-related hospital admissions	24 (1.9)	6 (0.5)**
Acute oral corticosteroid prescriptions[‖]		
0	1,145 (92.0)	1,132 (91.0)
1	74 (6.0)	95 (7.6)
≥2	25 (2.0)	17 (1.4)
Overall asthma control	1,105 (88.8)	1,105 (88.8)
Baseline SABA daily dose*,[¶]		
0 µg/day	902 (72.5)	902 (72.5)
1-100 µg/day	269 (21.6)	269 (21.6)
101-200 µg/day	50 (4.0)	50 (4.0)
>200 µg/day	23 (1.8)	23 (1.8)
Severe exacerbations		
0	1,127 (90.6)	1,127 (90.6)
≥1	117 (9.4)	117 (9.4)

Data are presented as n (%) unless otherwise stated.

GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist.

*Matching variable; [†]Evidence of rhinitis based on prescription of nasal corticosteroids during the baseline year or outcome analysis period; [‡]Evidence of GERD/GERD prophylaxis based on prescriptions of proton-pump inhibitors during the baseline year or outcome analysis period; [§]Evidence of oral candidiasis at baseline, identified as topical oral antifungal prescription for oral candidiasis; [‖]Acute oral corticosteroid prescription associated with asthma exacerbation treatment, defined as all courses that were definitely not maintenance therapy, AND/OR all courses where dosing instructions suggested exacerbation treatment (e.g. 6, 5, 4, 3, 2, 1 reducing, or 30 mg as directed), AND/OR all courses with no dosing instructions, but unlikely to be maintenance therapy, whereby maintenance therapy was defined as no evidence of reducing doses instructions, with a prescribed daily dose of <10 mg of prednisolone OR prescriptions of prednisolone tablets at a strength of 1 mg per day, with overall script coverage of more than 25% of days in a year; [¶]Calculated as (count of inhalers×doses in pack/365)×µg strength; **$P<0.01$; [††]$P≤0.001$.

significantly lower severe asthma exacerbation rates (adjusted rate ratio [95% CI], 0.69 [0.53-0.89]) and significantly greater odds of achieving risk-domain asthma control (defined as absence of asthma-related hospital admissions and of prescrip-tions of acute oral corticosteroids) and overall asthma control (defined as risk-domain asthma control plus average daily dose of ≤200 µg albuterol) than those receiving fine-particle ICS therapy, after adjusting for baseline confounders (Table 2 and Fig. 2).
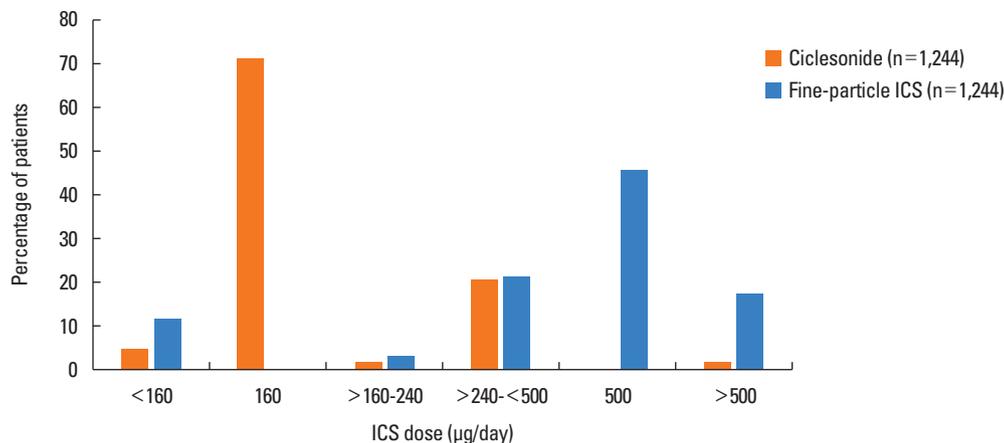
Fig. 1. Dose of inhaled corticosteroids prescribed at the initiation date. The doses of ciclesonide and fluticasone are reported as actual doses; the beclomethasone doses were halved and thus reported as fluticasone-equivalents, as per recommendations regarding corticosteroid equivalence.[1-3,6]

Table 2. Outcome measures during a 1-year period after ICS initiation

Characteristic	Treatment cohort		P value
	Ciclesonide n=1,244	Fine-particle ICS n=1,244	
No. of severe exacerbations			
0	1,123 (90.3)	1,065 (85.6)	<0.001
1-2	107 (8.6)	163 (13.1)	
3-4	11 (0.9)	11 (0.9)	
≥5	3 (0.2)	5 (0.4)	
Risk-domain asthma control, controlled	1,123 (90.3)	1,065 (85.6)	<0.001
Overall asthma control, controlled	1,075 (86.4)	947 (76.1)	<0.001
No. of asthma-related hospital admissions			
1	7 (0.6)	7 (0.6)	0.81
2	2 (0.2)	1 (0.1)	
SABA daily dose			
0 μg/day	733 (58.9)	487 (39.1)	<0.001
1-100 μg/day	305 (24.5)	309 (24.8)	
>100 μg/day	206 (16.6)	448 (36.0)	
Change in therapy at any time during outcome period*	329 (26.4)	416 (33.4)	<0.001
Controller-to-total medication ratio[†]			
<0.5	34 (2.7)	112 (9.0)	<0.001
0.5-<0.8	311 (25.0)	530 (42.6)	
0.8-<1	166 (13.3)	115 (9.2)	
1	733 (58.9)	487 (39.1)	
≥1 prescription of antifungal[‡]	29 (2.3)	19 (1.5)	0.14

Data are presented as n (%).
ICS, inhaled corticosteroid; SABA, short-acting β_2-agonist.
*Change in therapy during the outcome year was defined as an ICS dose increase of ≥50% or addition of new therapy including a leukotriene receptor antagonist, theophylline, or long-acting β_2-agonist; [†]The controller-to-total medication ratio was defined as the number of controller units/(number of controller units+number of reliever units), where controllers included ICS and LTRA; [‡]Antifungal medication definitely prescribed for treating oral candidiasis.

Secondary endpoints and other outcomes

Patients in the ciclesonide cohort received fewer prescriptions of other respiratory drugs and had significantly lower ICS daily dose exposure than the fine-particle ICS cohort during the out-come year (Table 3). The odds of a change in therapy during the outcome year were significantly lower for patients prescribed ciclesonide than those prescribed fine-particle ICS (adjusted odds ratio [95% confidence interval], 0.70 [0.59-0.83]). Similar-
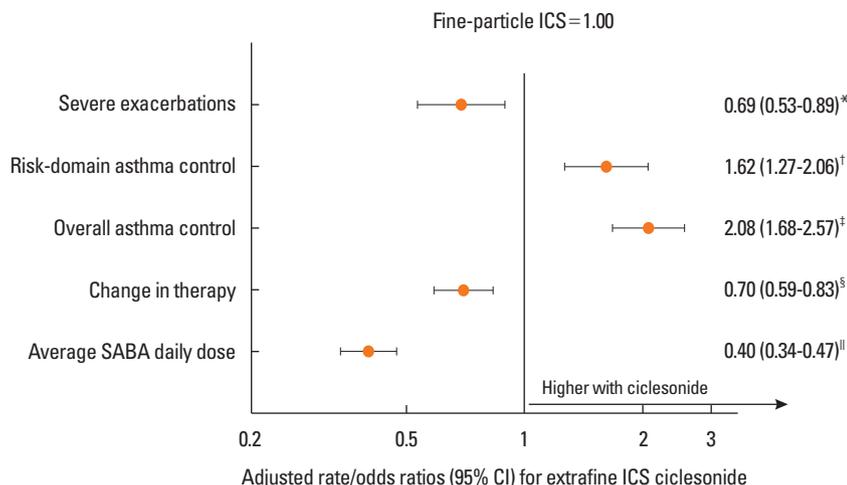
Fig. 2. Adjusted rate ratios (RRs) and odds ratios (ORs) for ciclesonide relative to fine-particle ICS during the 1 outcome year for the co-primary endpoints (severe exacerbation RR, risk domain asthma control OR, and overall asthma control OR) and secondary endpoints (change in therapy OR and daily short-acting β_2-agonist [SABA] use OR). *Adjusted for prescriptions of proton-pump inhibitors (yes/no) and baseline severe exacerbations (categorized); †Adjusted for age and prescriptions of proton-pump inhibitors (yes/no); ‡Adjusted for baseline overall asthma control and prescriptions of proton pump inhibitors (yes/no); §Adjusted for prescriptions of nasal corticosteroid preparations (yes/no); ‖Adjusted for age and baseline SABA daily dose.

Table 3. Respiratory drugs prescribed during the outcome year

Variable	Treatment cohort		P value
	Ciclesonide n = 1,244	Fine-particle ICS n = 1,244	
Acute oral corticosteroid courses, n (%)			
0	1,128 (90.7)	1,068 (85.9)	<0.001
1	77 (6.2)	123 (9.9)	
≥2	39 (3.1)	53 (4.3)	
SABA prescriptions, n (%)			
0	733 (58.9)	487 (39.1)	<0.001
1	240 (19.3)	231 (18.6)	
2	137 (11.0)	259 (20.8)	
≥3	134 (10.8)	267 (21.5)	
ICS daily dose exposure, median (IQR)*	126 (78-185)	332 (248-656)	<0.001
Average ICS daily dose exposure, n (%)*			
0-150 µg/day	760 (61.1)	382 (30.7)	<0.001
151-250 µg/day	299 (24.0)	478 (38.4)	
251-450 µg/day	143 (11.5)	215 (17.3)	
>450 µg/day	42 (3.4)	169 (13.6)	
ICS prescriptions, n (%)			
2	406 (32.6)	576 (46.3)	<0.001
3	275 (22.1)	240 (19.3)	
≥4	563 (45.3)	428 (34.4)	
≥1 LABA prescription, n (%)	559 (44.9)	666 (53.5)	<0.001
≥1 LTRA prescription, n (%)	52 (4.2)	38 (3.1)	0.13

ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist.
*ICS daily dose exposure calculated as (count of inhalers × doses in pack/365) × µg strength, using actual doses for ciclesonide and fluticasone-equivalent doses for fine-particle ICS, as per recommendations for corticosteroid equivalence.[1-3,6]

ly, the odds of being prescribed a higher SABA dose during the outcome period significantly favored the ciclesonide cohort (Table 2 and Fig. 2). Subanalysis results for the patients with evidence of rhinitis (prescribed nasal corticosteroids) were similar to those of the main analysis (Supplementary Table 2).

During the outcome year, patients prescribed ciclesonide received a significantly higher ratio of controller-to-total medication than those prescribed fine-particle ICS (Table 2). Although patients in the ciclesonide cohort had higher hospital admissions during the baseline year compared with those receiving fine-particle ICS (1.9% vs 0.5%; *P*=0.002), this difference was no longer observed during the outcome year after ICS initiation (0.7% vs 0.6% patients prescribed fine-particle ICS; *P*=0.81; Table 2).

Prescriptions of oral antifungal medications for treating oral candidiasis were similar in both treatment cohorts at baseline and during the outcome year.

DISCUSSION

In our population-based matched cohort study, we observed that patients prescribed extrafine-particle ciclesonide experienced significantly lower rates of severe exacerbations, *i.e.*, hospitalizations or acute oral corticosteroid courses, in the first year after initiating ICS treatment than those prescribed fine-particle ICS, and ciclesonide prescribing was associated with better odds of achieving asthma control. Patients prescribed ciclesonide were also significantly less likely to require a change in therapy or higher doses of reliever medication than those prescribed fine-particle ICS. Notably, the prescribed doses of ciclesonide were one-third those of fine-particle ICS at the initiation date despite matching for patient characteristics (median dose, 160 vs 500 μg/day); and ICS dose exposure during the outcome year was also significantly lower for the ciclesonide cohort (median, 126 vs 332 μg/day). The drop in the dose of both ICS from the initial prescribed dose was likely the result of incomplete adherence during the outcome year, a common finding in real life.[31]

We matched the cohorts for important clinical asthma parameters, including baseline risk-domain asthma control status (capturing asthma-related hospitalizations and oral corticosteroid bursts during the baseline year), baseline SABA dose, and demographic characteristics (sex and age). Nevertheless, the ciclesonide cohort presented with signs of more difficult-to-control asthma at baseline in the form of greater frequency of nasal corticosteroid and proton pump inhibitor prescriptions.[1,32] This would presumably favor better asthma control in the outcome year for the fine-particle ICS cohort. Moreover, despite higher baseline hospital admissions in the ciclesonide than in the fine-particle ICS cohort, there was no difference in outcome hospitalizations. These findings suggest a clinically significant improvement in asthma control for patients prescribed ciclesonide who had unstable disease and thus would

classically be excluded from randomized controlled trials.

Possible mechanisms to explain better effectiveness of ciclesonide include (1) improved airway drug distribution, including small airways[4,7,8,10]; (2) decreased impact of errors in inhalation techniques (especially poor coordination or too fast inhalation flow rate) on lung deposition[33,34]; and (3) improved adherence, promoted by greater perception of treatment effects, once daily dosing, or reassurance as to the dose of corticosteroid. Moreover, compared to those prescribed fine-particle ICS, more patients prescribed ciclesonide had a controller-to-total medication ratio of ≥0.5, a finding associated with improved asthma-related quality of life, better disease control, and reduced symptoms.[35]

There are several limitations to this study. Exclusion of patients without data during a 1-year period before and 1 year after ICS initiation meant that patients who moved or died were not represented. The requirement that all patients have 1-year outcome data predisposed the study to survivor bias. However, this may not have had a major effect, given the median age of 45 years and because patients prescribed their first ICS are unlikely to have severe asthma. Other limitations are those common to observational studies: biases deriving from unmeasured confounders that may particularly affect 1 of the 2 treatment strategies, non-random assignment of drug treatment, and potential misclassification bias and under-reporting if medical attention was not sought.

During the study period, ciclesonide was not the most common ICS prescribed in the Netherlands, although it was prescribed for 34% of patients. Thus, there may be unrecorded reasons physicians chose to prescribe ciclesonide, resulting in prescription bias. This channeling phenomenon was suggested given that patients prescribed ciclesonide had signs of difficult-to-treat asthma (rhinitis and gastroesophageal reflux),[32] findings potentially reducing positive effects of ciclesonide versus fine-particle ICS on asthma outcomes, which was not the case. While 1,244/1,382 (90%) eligible patients initiating ciclesonide were matched, only 1,244/2,682 (46%) of those initiating fine-particle ICS were matched, suggesting the possibility that patients in the fine-particle cohort were not representative of those who initiate fine-particle ICS therapy in the Netherlands.

Finally, our analyses were limited by data availability; for example, smoking history, which may have some impact on effectiveness of ICS,[17,36] was not available, and nor were body mass index and lung function data. Diagnostic information was inferred from prescribing data. This meant that patients were selected as having asthma based on prescribed therapy, potentially leading to diagnostic misclassification. To mitigate this, we excluded patients with only 1 ICS prescription, which could have been a therapy trial. We were not able to assess current clinical control, but SABA dose (based on prescriptions) served as an indication of symptom control: 83% and 64% of patients in the ciclesonide and fine-particle ICS cohorts, respectively,

were prescribed ≤1 puff/day (≤100 µg/day) of SABA on average, well within the definition of good control of asthma from an administrative database.[37] The actual use of SABA was likely lower, as patients tend to have multiple inhalers and do not use all of the prescribed canisters.

This study also has several strengths. Patients were drawn from a large diverse population with subsequent 1:1 exact matching on key baseline characteristics to ensure that the 2 cohorts were as comparable as possible with respect to demographic and clinical characteristics.[30] Outcome measures were adjusted for appropriate non-collinear baseline confounders. The 1-year baseline and outcome periods enabled us to identify measurable changes in endpoints, such as hospitalizations, severe exacerbations, and asthma control, and also to allow for seasonal changes in respiratory conditions. All patients were prescribed the same inhaler type for ICS (pMDI), minimizing outcome differences associated with inhalation techniques for ICS or mixing inhaler devices (most SABA inhalers prescribed in the Netherlands are pMDIs).[6,38]

The residual baseline differences between treatment cohorts after matching (*i.e.*, greater frequency of rhinitis and gastroesophageal reflux prescriptions in the ciclesonide treatment cohort) were addressed in the statistical models. Nasal corticosteroid prescriptions were not significant in the statistical model for the co-primary endpoints, suggesting that these did not affect the results, and the subgroup analysis of patients receiving nasal corticosteroid prescriptions corroborated the main findings. The co-primary endpoints were all adjusted for proton pump inhibitor prescriptions.

Guidelines recommend that fluticasone and ciclesonide be prescribed at similar nominal doses[1-3,6,15] based on equipotence in formal testing in randomized trials. Despite these recommendations, we found that in practice, ciclesonide was prescribed at lower doses than fluticasone and that fluticasone was typically prescribed at higher than recommended doses, corroborating findings from prior studies in the Netherlands, as well as New Zealand, the UK, and the USA.[21,22,39,40] Lower doses of ICS may be associated with reduced adverse events;[41,42] further research is required to determine whether the lower prescribed doses of ciclesonide and of extrafine-particle beclomethasone in prior studies[21,22] are associated with fewer adverse events in real-life populations, an important consideration for long-term asthma controller therapies and one that requires further studies, as we could not capture drug-related adverse events from our data source. Extrafine-particle ICS have relatively low oropharyngeal deposition, which could potentially lead to fewer oral side effects than with larger particle ICS.[8,15,18,43] However, we found that the proportion of patients prescribed antifungal medication for oral candidiasis was low and similar in the ciclesonide and fine-particle ICS treatment cohorts (2.3% vs 1.5%).

In conclusion, the results of this matched cohort analysis suggest that initiation of ICS with ciclesonide is associated with better 1-year asthma outcomes and fewer changes to therapy in that year, at one-third of the prescribed dose than with fine-particle ICS. The study drew on reliable dispensing and hospitalization data for a real-life Dutch population—presumably including smokers and non-smokers, patients with good and bad inhaler techniques, stable and unstable asthma, and good and bad adherence. The association of better outcomes with ciclesonide therapy was present, even though asthma was somewhat more severe in those prescribed ciclesonide. More real-life observational or randomized controlled studies of other patient populations and different extrafine-particle ICS are needed to further explore these findings.

REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention, revised 2014 [Internet]. [place unknown]: Global Initiative for Asthma; 2014 [cited 2016 Apr 28]. Available from: http://www.ginasthma.org.
2. British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline (SIGN 141) [Internet]. London: British Thoracic Society; 2014 [cited 2016 Apr 28]. Available from: http://www.sign.ac.uk/pdf/SIGN141.pdf.
3. National Heart, Lung, and Blood Institute (US). Expert panel report 3: guidelines for the diagnosis and management of asthma: national asthma education and prevention program [Internet]. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 [cited 2016 Apr 28]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
4. Usmani OS. Small airways dysfunction in asthma: evaluation and management to improve asthma control. Allergy Asthma Immunol Res 2014;6:376-88.

5. Lipworth B. Targeting the small airways asthma phenotype: if we can reach it, should we treat it? Ann Allergy Asthma Immunol 2013; 110:233-9.

6. Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, et al. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J 2011;37:1308-31.

7. Newman S, Salmon A, Nave R, Drollmann A. High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma. Respir Med 2006;100:375-84.

8. Leach CL, Bethke TD, Boudreau RJ, Hasselquist BE, Drollmann A, Davidson P, et al. Two-dimensional and three-dimensional imaging show ciclesonide has high lung deposition and peripheral distribution: a nonrandomized study in healthy volunteers. J Aerosol Med 2006;19:117-26.

9. Cohen J, Douma WR, ten Hacken NH, Vonk JM, Oudkerk M, Postma DS. Ciclesonide improves measures of small airway involvement in asthma. Eur Respir J 2008;31:1213-20.

10. Hoshino M. Comparison of effectiveness in ciclesonide and fluticasone propionate on small airway function in mild asthma. Allergol Int 2010;59:59-66.

11. Cohen J, Postma DS, Douma WR, Vonk JM, De Boer AH, ten Hacken NH. Particle size matters: diagnostics and treatment of small airways involvement in asthma. Eur Respir J 2011;37:532-40.

12. Thompson BR, Douglass JA, Ellis MJ, Kelly VJ, O'Hehir RE, King GG, et al. Peripheral lung function in patients with stable and unstable asthma. J Allergy Clin Immunol 2013;131:1322-8.

13. van der Wiel E, ten Hacken NH, Postma DS, van den Berge M. Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review. J Allergy Clin Immunol 2013;131:646-57.

14. Manoharan A, Anderson WJ, Lipworth J, Ibrahim I, Lipworth BJ. Small airway dysfunction is associated with poorer asthma control. Eur Respir J 2014;44:1353-5.

15. Manning P, Gibson PG, Lasserson TJ. Ciclesonide versus other inhaled steroids for chronic asthma in children and adults. Cochrane Database Syst Rev 2008:CD007031.

16. Dahl R, Engelstätter R, Trebas-Pietraś E, Kuna P. A 24-week comparison of low-dose ciclesonide and fluticasone propionate in mild to moderate asthma. Respir Med 2010;104:1121-30.

17. Price D, Bjermer L, Popov TA, Chisholm A. Integrating evidence for managing asthma in patients who smoke. Allergy Asthma Immunol Res 2014;6:114-20.

18. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Influence of particle size and patient dosing technique on lung deposition of HFA-beclomethasone from a metered dose inhaler. J Aerosol Med 2005;18:379-85.

19. Price D, Bateman ED, Chisholm A, Papadopoulos NG, Bosnic-Anticevich S, Pizzichini E, et al. Complementing the randomized controlled trial evidence base. Evolution not revolution. Ann Thorac Soc 2014;11 Suppl 2:S92-8.

20. Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martin RJ, et al. Integrating real-life studies in the global therapeutic research framework. Lancet Respir Med 2013;1:e29-30.

21. Price D, Martin RJ, Barnes N, Dorinsky P, Israe lE, Roche N, et al. Prescribing practices and asthma control with hydrofluoroalkane-beclomethasone and fluticasone: a real-world observational study. J Allergy Clin Immunol 2010;126:511-518.e1-10.

22. Colice G, Martin RJ, Israel E, Roche N, Barnes N, Burden A, et al. Asthma outcomes and costs of therapy with extrafine beclometha-

23. PHARMO [Internet]. Utrecht: PHARMO; [cited 2016 Apr 28]. Available from: http://www.pharmo.nl/.

24. Herk-Sukel MP, Lemmens VE, Poll-Franse LV, Herings RM, Coebergh JW. Record linkage for pharmacoepidemiological studies in cancer patients. Pharmacoepidemiol Drug Saf 2012;21:94-103.

25. Herings RM, Pedersen L. Pharmacy-based medical record linkage systems. In: Strom BL, Kimmel SE, Hennessy S, editors. Pharmacoepidemiology. 5th ed. Chichester: Wiley-Blackwell; 2012. 270-86.

26. Roche N, Reddel H, Martin R, Brusselle G, Papi A, Thomas M, et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. Ann Am Thorac Soc 2014;11 Suppl 2:S99-104.

27. Respiratory Effectiveness Group (UK) [Internet]. Cambridge: Respiratory Effectiveness Group; [cited 2015 Dec 7]. Available from: http://www.effectivenessevaluation.org/.

28. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The European Union electronic register of post-authorisation studies (EU PAS Register) [Internet]. London: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; [cited 2016 Apr 28]. Available from: http://www.encepp.eu/encepp/studiesDatabase.jsp.

29. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.

30. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci 2010;25:1-21.

31. Sadatsafavi M, Fitz Gerald M, Marra C, Lynd L. Costs and health outcomes associated with primary vs secondary care after an asthma-related hospitalization: a population-based study. Chest 2013; 144:428-35.

32. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126:466-76.

33. Newman SP, Pavia D, Garland N, Clarke SW. Effects of various inhalation modes on the deposition of radioactive pressurized aerosols. Eur J Respir Dis Suppl 1982;119:57-65.

34. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. Am J Respir Crit Care Med 2005;172:1497-504.

35. Schatz M, Zeiger RS, Vollmer WM, Mosen D, Mendoza G, Apter AJ, et al. The controller-to-total asthma medication ratio is associated with patient-centered as well as utilization outcomes. Chest 2006; 130:43-50.

36. Roche N, Postma DS, Colice G, Burden A, Guilbert TW, Israel E, et al. Differential effects of inhaled corticosteroids in smokers/ex-smokers and nonsmokers with asthma. Am J Respir Crit Care Med 2015;191:960-4.

37. Schatz M, Zeiger RS, Vollmer WM, Mosen D, Apter AJ, Stibolt TB, et al. Validation of a beta-agonist long-term asthma control scale derived from computerized pharmacy data. J Allergy Clin Immunol 2006;117:995-1000.

38. Price D, Chrystyn H, Kaplan A, Haughney J, Román-Rodríguez M, Burden A, et al. Effectiveness of same versus mixed asthma inhaler devices: a retrospective observational study in primary care. Allergy Asthma Immunol Res 2012;4:184-91.

39. Black PN, Lawrence BJ, Goh KH, Barry MS. Differences in the po-

tencies of inhaled steroids are not reflected in the doses prescribed in primary care in New Zealand. Eur J Clin Pharmacol 2000;56:431-5.

40. Schirm E, de Vries TW, Tobi H, van den Berg PB, de Jong-van den Berg LT. Prescribed doses of inhaled steroids in Dutch children: too little or too much, for too short a time. Br J Clin Pharmacol 2006;62: 383-90.

41. van der Molen T, Foster JM, Caeser M, Müller T, Postma DS. Differ-

ence between patient-reported side effects of ciclesonide versus fluticasone propionate. Respir Med 2010;104:1825-33.

42. McKeever T, Harrison TW, Hubbard R, Shaw D. Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case-control study. Chest 2013;144:1788-94.

43. Nave R, Watz H, Hoffmann H, Boss H, Magnussen H. Deposition and metabolism of inhaled ciclesonide in the human lung. Eur Respir J 2010;36:1113-9.