Early View

Research letter

The Effect of Type and Dosage of Newly Prescribed Inhaled Corticosteroids on Obstructive Lung Disease and Pneumonia Hospitalisations in Older Individuals with Asthma, Chronic Obstructive Pulmonary Disease (COPD) or Both: A Retrospective Study of Health Administrative Data

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Running Title: The effect of ICS on Obstructive Lung Disease and Pneumonia Hospitalizations in Older Individuals with Asthma and/or COPD

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TAKE HOME MESSAGE

Our study suggested a less favourable safety-effectiveness profile for fluticasone compared to budesonide and other inhaled corticosteroids (ICS) in elderly individuals with asthma, COPD or both. Higher doses of ICS were not associated with improved effectiveness in these populations.

The safety and risk-benefit profiles associated with different types and dosages of inhaled corticosteroids (ICS) in older individuals with asthma and COPD remain unknown [1, 2]. Limited evidence suggests that adults with asthma prescribed medium or high ICS doses are at risk of clinically important systemic side effects that do not plateau with higher doses as efficacy outcomes do [3]. Older patients with COPD have been shown to have increased risk of pneumonia with both budesonide and fluticasone [4]; however, the risk seems greater in the latter [2, 4-6].

Our objective was to determine whether specific types or dosages of ICS were differentially associated with rates of hospitalization for obstructive lung disease and pneumonia in older new users of ICS with asthma or COPD.

For this retrospective longitudinal population study we utilized provincial health administrative data from all insured individuals aged 66 and older living in Ontario Canada between 2003 and 2014 who met a validated case definition of physician-diagnosed COPD (***COPD cohort***) and/or asthma (***asthma cohort***) and were ***new ICS users*** (as determined by a preceding one-year ICS-free period) [7]. Full definitions of the population of interest, exposure and covariates are reported elsewhere [8]. Overlap in COPD and asthma was examined by stratifying individuals with each (COPD or asthma) by a history of the other defined as one or more previous ambulatory care visits, emergency department visits or hospitalizations. Ethics approval was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada.

The ICS receipt date was the ***index date***. ***ICS types*** were categorized as (i) budesonide, (ii) fluticasone, and (iii) other (beclomethasone, ciclesonide or mometasone). ***Initial ICS daily dosages*** were converted

to their equivalent fluticasone dosage [9, 10] -- for descriptive purposes, they were categorized as low

(≤250 mcg), moderate (251-500 mcg), and high (>500 mcg) [11].

We followed included individuals from their index dates to death, an outcome of interest or March 31st,

2015, at which point they were censored. The primary outcome was hospitalization for pneumonia;

secondary outcome hospitalization for asthma or COPD.

We considered important covariates [8], including individual demographics, comorbidities, disease

severity, medications, oxygen, long-term positive airway pressure treatment, primary and specialist

care, flu vaccination, and spirometry (**Table 1**).

To investigate the relationship between ICS type and dosages and the outcomes of interest, we used

multivariable Cox-proportional hazards regressions adjusted for all covariates including ICS type or

dosage at the index date, as applicable, and the ICS coverage in follow-up. We modelled the

fluticasone-equivalent daily ICS dose continuously using restricted cubic spline transformation. As

hypothesized *a priori,* we stratified the asthma population by a history of COPD and the COPD

population by a history of asthma [8]. Statistical analyses were performed using R version 2.15.2.

Of 87,690 individuals with physician-diagnosed asthma (27% with concurrent COPD), 42,031 (48%)

were new ICS users: median age of 70 (interquartile range [IQR]: 67-77 years): 33% men. Of 150,593

individuals with physician-diagnosed COPD (25% with a history of asthma), 47,557 (32%) were new

ICS users: median age of 75 (IQR: 70-82 years): 50% men.

Over a median follow-up of 5.4 years (IQR: 2.5-8.9), of 42,031 asthma ICS new users, 4,854 (12%)

were hospitalized at least once for asthma or COPD, and 4,990 (12%) were hospitalized at least once

for pneumonia. Over a median follow-up of 3.7 years (IQR: 1.6-6.8), of 47,557 COPD who ICS new users, 12,905 (27%) were hospitalized for asthma or COPD, and 10,872 (23%) were hospitalized for pneumonia.

Asthma ICS new users received a median of 750 mcg of fluticasone equivalents/day (IQR: 500-1,000 mcg), with 59% using >500 mcg and 41% ≥ 1,000 mcg daily. ICS treatment was initiated with budesonide in 29% of patients, with fluticasone in 65%, and with another ICS in 6%. In adjusted analyses, higher ICS dose (1,000 mcg vs. 500 mcg) was not associated with a higher risk of pneumonia hospitalizations (HR 1.04, 95% CI 0.98-1.09) and did not reduce asthma or COPD hospitalization for (HR 1.05, 95% CI 0.99-1.11) (**Table 1**). Compared to fluticasone, budesonide was associated with fewer pneumonia hospitalizations (adjusted HR 0.88, 95% CI 0.82-0.94) and with fewer asthma or COPD hospitalizations (HR 0.79, 95% CI 0.74-0.85). Receipt of other ICS was also associated with fewer asthma or COPD hospitalizations (HR 0.71, 95% CI 0.60-0.85).

COPD ICS users received a median of 750 mcg fluticasone equivalents/day (IQR 500-1,000 mcg) with 60% using >500 mcg and with 45% using at ≥ 1,000 mcg. ICS treatment was initiated with budesonide in 22% of patients, with fluticasone in 74% and another ICS in 4%. In adjusted analyses, a higher ICS dose (1,000 mcg vs. 500 mcg) was associated with a higher risk for pneumonia hospitalization (HR 1.06, 95% CI 1.02-1.10) but not a reduction in asthma or COPD hospitalizations (HR 1.04, 95% CI 1.00-1.07) (**Table 1**). Compared to fluticasone, budesonide (HR 0.88, 95% CI 0.83-0.92) and other ICS (HR 0.77, 95% CI 0.69-0.87) were associated with fewer pneumonia hospitalizations. Budesonide (HR 0.80, 95% CI 0.77-0.84) and other ICS (HR 0.71, 95% CI 0.63-0.79) were also associated with fewer asthma or COPD hospitalizations than fluticasone.

Results in individuals with concurrent COPD and asthma were similar to those in subjects with COPD or asthma alone in both populations confirmed also by nonsignificant interactions terms (p values>0.1).

Our findings are consistent with previous studies showing a higher risk of pneumonia associated with an increased daily ICS dose in individuals with COPD [6, 12]. They are also consistent with other studies showing more favourable safety-effectiveness profiles for budesonide and other ICS compared to fluticasone [2, 13]. This may be explained by differences in pharmacology and pharmacokinetics between medications [14]. It has been suggested that fluticasone may increase risk of pneumonia because of higher lipophilicity and slower dissolution rate [13]. Despite plausible mechanisms and adjustment for dosage, however, we cannot exclude confounding due to fluticasone being more likely to be prescribed in higher dosages in individuals with more severe disease.

Our study has several limitations. First, individuals with poor adherence or poor control on existing medications may be overrepresented among new users, and the "new users" study design may give excessive weight to short-term users [15]. Further, early symptoms of pneumonia could be misclassified as a COPD exacerbation prompting the use of ICS, incorrectly attributing them to pneumonia; however, this bias would apply to all groups, and we did not see an increase in pneumonia in all groups. Unmeasurable variables could also confound study results such a symptom severity, lung function, smoking and blood eosinophil levels. Further, there was a possibility of confounding by indication if clinicians were more likely to prescribe fluticasone to sicker patients than other ICS. To minimize this, we employed a new users design and adjusted for multiple factors that were proxies of COPD or asthma severity.

Among older adults with physician-diagnosed COPD who were new users of ICS, higher ICS dose was associated with increased risk of pneumonia hospitalizations, but not with reduced risk of obstructive

lung disease hospitalizations. Fluticasone appears to have a less favourable safety-effectiveness profile compared to other ICS in older individuals with asthma, COPD, or both. Our study adds important findings to the growing body of evidence on the relative magnitudes of risks and benefits according to ICS type and dose. This practical knowledge can be used by health professionals to optimize safe medication use and health outcomes in individuals with obstructive lung disease receiving ICS for the first time in later life.

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AUTHOR'S CONTRIBUTIONS

All co-authors were involved in the following: study conception and design, interpretation of data, revising the manuscript critically for the accuracy and important intellectual content, and final approval of the version to be published.

Dr. Tetyana Kendzerska additionally was involved in the following: literature search, obtaining administrative data, analyses of data and drafting of the manuscript.

Dr. Andrea Gershon additionally was involved in ethics board' application, obtaining administrative data, analyses of data and drafting of the manuscript.

Drs. Andrea Gershon and Tetyana Kendzerska had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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None of the sources had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or in the decision to submit the report for publication.

CONFLICT OF INTEREST DECLARATION

All authors declare that no competing interests exist.

DATA AVAILABILITY

In Ontario (Canada), details on virtually all physician and hospital services are captured in health administrative databases housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences). For the current study, these databases were linked on an individual level using unique encoded identifiers. The resulting dataset is held securely in coded form at the ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. A full data set creation plan for the study is available from the authors upon request.

IRB APPROVAL

Ethics approval was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. A waiver of informed consent was obtained.

Table 1. The effect of the ICS dosages/type on the outcomes, obstructive lung disease and pneumonia hospitalizations, adjusted for baseline differences, including the type/dosage of the ICS and year of the ICS prescription (effects expressed as hazard ratios [HR] and 95% confidence interval [CI])*.

Initial ICS dosages and type	Obstructive lung disease hospitalizations	Pneumonia hospitalizations
	Adjusted HR (95% CI)	**Adjusted HR (95% CI)**
Physician-diagnosed asthma		
ICS dosages		
1,000 vs 500 mcg# of fluticasone equivalent dosage	1.05 (0.99-1.11)	1.04 (0.98-1.09)
ICS types		
Budesonide vs. fluticasone	**0.79 (0.74-0.85)**	**0.88 (0.82-0.94)**
Other ICS vs. fluticasone	**0.71 (0.60-0.85)**	0.90 (0.77-1.06)
Physician-diagnosed COPD		
ICS dosages		
1000 vs 500# mcg of fluticasone equivalent dosage	1.04 (1.00-1.07)	**1.06 (1.02-1.10)**
ICS types		
Budesonide vs. fluticasone	**0.80 (0.77-0.84)**	**0.88 (0.83-0.92)**
Other ICS vs. fluticasone	**0.71 (0.63-0.79)**	**0.77 (0.69-0.87)**

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long-acting anticholinergics; SAMA, short-acting anticholinergics

In bold – statistically significant effect

*Variables included in the statistical model were demographics at baseline (age, sex, socioeconomic, rural and immigrant status, being in long-term care), prior comorbidities (frailty, CV hospitalizations, hypertension, diabetes, gastroesophageal reflux disease, atopy, mental health condition, dementia, cancer, osteoporosis, cataracts), prior disease severity (asthma and COPD hospitalizations in the last five years), medications in the last year prior to the index date (LABA, LAMA, SABA, SAMA, oral corticosteroids, respiratory-related antibiotics, proton pump inhibitors, CV medications), ICS dosages/type at the index date, ICS coverage in follow-up, prior utilization of supplemental oxygen, long-term positive airway pressure treatment, primary and specialist care, flu vaccination, and spirometry.

comparing 75th to 25th percentile

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