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Discontinuation of Inhaled Corticosteroids in COPD and the Risk Reduction of Pneumonia

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BACKGROUND: The widespread use of inhaled corticosteroids (ICSs) for COPD treatment has been questioned. Recent studies of weaning some patients with COPD off ICSs found little or no adverse consequences compared with long-acting bronchodilators. It is unclear, however, whether discontinuation of ICSs reduces the elevated risk of pneumonia associated with these drugs.

METHODS: Using the Quebec health insurance databases, we formed a new-user cohort of patients with COPD treated with ICSs during 1990 to 2005 and followed through 2007 or until a serious pneumonia event, defined as a first hospitalization for or death from pneumonia. A nested case-control analysis of the cohort was used to estimate the rate ratio of serious pneumonia associated with discontinuation of ICS use compared with continued use, adjusted for age, sex, respiratory disease severity, and comorbidity.

RESULTS: The cohort included 103,386 users of ICSs, of whom 14,020 had a serious pneumonia event during 4.9 years of follow-up (incidence rate, 2.8/100/y). Discontinuation of ICSs was associated with a 37% decrease in the rate of serious pneumonia (rate ratio [RR], 0.63; 95% CI, 0.60-0.66). The risk reduction was rapidly evident, going from 20% in the first month to 50% by the fourth month after discontinuation. The risk reduction was particularly marked with fluticasone (RR, 0.58; 95% CI, 0.54-0.61) but less so with budesonide (RR, 0.87; 95% CI, 0.78-0.97).

CONCLUSIONS: Discontinuation of ICS use in COPD is associated with a reduction in the elevated risk of serious pneumonia, particularly so with fluticasone.

CHEST 2015; 148(5):1177-1183

Manuscript received March 13, 2015; revision accepted June 1, 2015; originally published Online First June 25, 2015.

ABBREVIATIONS: ICS = inhaled corticosteroid; RAMQ = Régie de l'assurance maladie du Québec; RR = rate ratio

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FUNDING/SUPPORT: This research was funded in part by a grant from the Canadian Institutes of Health Research [CIHR MOP-49462] and the Canadian Foundation for Innovation [CFI 94480]. Dr Suissa is the recipient of the James McGill Professorship award.

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DOI: 10.1378/chest.15-0627

Inhaled corticosteroids (ICSs) have been used widely over the last decade to treat COPD. Although treatment guidelines suggest that they be added to long-acting bronchodilators and introduced only for patients at high risk of exacerbation,[1] ICSs are currently used by up to 85% of patients treated for COPD.[2] Although ICS use may be appropriate for the exacerbation-prone patients, it may not be applicable for a large number of the remaining patients, including most with mild or moderate COPD.[3,4] Recent trials have, therefore, assessed the effects of weaning these patients with COPD off ICSs, finding little or no adverse consequences after they were discontinued and replaced by long-acting bronchodilators.[5,6]

A major impetus for discontinuing ICSs when unnecessary is to avoid their systemic side effects, particularly the increased risk of pneumonia.[7-10] The trials of ICS withdrawal only aimed to study potential changes in effectiveness of therapy, assuming that discontinuation of ICSs would reduce the risk of pneumonia. However, the resulting data on pneumonia are ambiguous. In the largest randomized trial of ICS discontinuation, pneumonia occurred in 5.8% of patients who continued fluticasone treatment compared with 5.5% for those patients assigned to discontinue fluticasone over the 12-month follow-up.[6] This nonsignificant 5% reduction in the risk of pneumonia (rate ratio [RR], 0.95; 95% CI, 0.67-1.33) does not corroborate the anticipated risk reduction associated with ICS withdrawal in COPD. In this article, we assess the effect of ICS discontinuation in COPD on the incidence of serious pneumonia using a large population-based cohort with prolonged follow-up.

Materials and Methods

Data Source

We used the computerized databases of the Régie de l'assurance maladie du Québec (RAMQ), which manages the universal health insurance program of the seven million residents of the province of Quebec, Canada. The databases contain information on demographics and all medical services given to its residents. The prescription drugs database includes outpatient prescription medications dispensed to all people aged ≥ 65 years, social welfare recipients, and, since 1996, all other residents who opted to join the provincial drug plan, covering around one-half the population of Quebec. All deaths are obtained from the Institut de la statistique du Québec database, containing the date of death and the underlying cause of death. These linkable databases have been used previously to conduct epidemiologic studies of the risks of ICSs, including pneumonia.[8,10-15]

Study Design

The source population for this study consisted of all subjects who, between 1990 and 2005, were dispensed at least one prescription for a respiratory medication among β-agonists, theophylline, ipratropium or tiotropium bromide, and ICSs. The base cohort of patients with COPD, used in a previous study of the risk of pneumonia, was defined by all subjects with three or more prescriptions for these medications (except ICSs) in any 1 year and on at least two different dates.[10] To ensure a new-user cohort, we excluded patients with any respiratory medication during the 2 years before the first of the three prescriptions. Subjects were at least 55 years old and had to have 1 year of drug coverage by the time of their third prescription. Subjects using nedocromil, ketotifen, cromolyn, or antileukotrienes, or with a primary or secondary diagnosis of asthma during a hospitalization, were excluded.

To evaluate the effect of ICS discontinuation, we defined the study cohort as all subjects from the base cohort who initiated ICS treatment on or after the date of the third cohort-defining prescription. The date of this first ICS prescription was taken as cohort entry, and patients were followed until the occurrence of the pneumonia outcome, the end of RAMQ drug coverage, death, or March 31, 2007. In view of the large size of the cohort and the large number of outcome events, as well as the time-varying nature of ICS prescriptions, we used a nested case-control analysis within the study cohort.

Pneumonia Cases and Control Subjects

Serious pneumonia was defined as a hospitalization for or death from pneumonia. The first hospitalization with an admission diagnosis or primary diagnosis of pneumonia of any cause, including influenza, was identified in the RAMQ hospitalization database (*International Classification of Diseases, 9th revision* codes 480 to 487.0, *International Classification of Diseases, 10th revision* codes J10.0, J11.0, J12-J18) during cohort follow-up. For outpatients, deaths with pneumonia as a principal cause were identified. The date of admission or outpatient death was called the index date.

For each case, 10 control subjects matched on the case subject's age within 1 year and on cohort entry month were selected at random from all subjects without the outcome of interest by the time of the event date (index date) of the case. When cases had no eligible control subjects, the age and calendar time matching criteria were expanded, and when fewer than 10 potential control subjects were available for a case, all subjects in the matched set were included as control subjects for that case.

ICS Discontinuation

All prescriptions for ICSs, alone or in a combination inhaler, dispensed during follow-up were identified. These include inhaled beclomethasone, fluticasone, budesonide, triamcinolone, and flunisolide. The duration of each ICS prescription was used to define current use as a prescription duration that covers the index date. For noncurrent users, the duration of discontinuation was defined as the time from the end of the last prescription before the index date until the index date. In addition, the time from the first ICS prescription until the index date (for the current users) or until discontinuation (for the noncurrent users) was used to measure the degree of adherence, quantified as the proportion of this time covered by ICS prescriptions. A cut-point of 80% was used to define satisfactory adherence.

Data Analysis

Crude and adjusted RRs of serious pneumonia associated with discontinued ICS use, relative to current use, and 95% CIs were estimated by conditional logistic regression to account for the matching of cases and control subjects. The RRs were adjusted for age (matched by design), sex, and severity of respiratory disease, as well as other conditions associated with a risk of pneumonia. Severity of respiratory disease was measured by the number of prescriptions for β-agonists, ipratropium and tiotropium bromide, theophylline, oral corticosteroids, and antibiotics, and the presence of a hospitalization with a primary diagnosis of COPD, all measured in the year prior to the index date. We excluded antibiotic prescriptions in the 30 days prior to the index date, since this could represent initial therapy for the pneumonia under study, but included oral corticosteroids during this recent time period. Comorbidity included cardiac disease defined by a prescription for cardiotropic