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REVIEW

Clinical effectiveness of inhaled corticosteroids versus montelukast in children with asthma: prescription patterns and patient adherence as key factors

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Abstract

Objectives:
To examine the real-life effectiveness of inhaled corticosteroids (ICS) versus leukotriene receptor antagonists (LTRA) monotherapy in children with mild or moderate asthma.

Methods:
Using medical and drug records, we accrued a cohort of 227 children aged 2–17 years, prescribed daily LTRA or ICS monotherapy. LTRA-treated children were matched on age, gender, and previous acute-care visits in a 1:3 ratio to ICS-treated children. Outcomes included rescue oral corticosteroids, prescription duration and dispensing, acute-care visits, hospital admissions, and β_2-agonist use.

Results:
More ICS- than montelukast-treated children had persistent asthma (73 vs. 50%) and fewer had good asthma control (35 vs. 61%) at baseline, suggesting residual confounding by indication. Physician prescriptions covered 62% of the follow-up period for ICS compared to 97% for montelukast (mean group difference [MGD]: −17%, 95% CI: −28%, −7%). In pharmacies, patients claimed 51 vs. 74% of prescribed ICS and montelukast, respectively (MGD = −12% [−20%, −4%]). Consequently, dispensed ICS and montelukast covered 24% and 38% of follow-up period, respectively (MGD = −14% [−22%, −6%]). No group differences in oral corticosteroids (RR = 1.10 [0.66, 1.84]) and acute-care visits (RR = 1.79 [0.96, 3.34]) were observed. ICS-treated children experienced more hospital admissions (RR = 3.63 [1.20, 11.03]) and needed more frequently rescue β_2-agonist use of ≥4 doses per week (RR = 2.54 [1.23, 5.23]).

Conclusions:
When compared to LTRA, the prescription of ICS monotherapy did not significantly reduce rescue oral corticosteroids or acute care visits and was associated with a higher rate of hospital admission for asthma and rescue β_2-agonist use. The findings may be due to paradoxical shorter ICS prescription duration and lower patient adherence, despite more persistent asthma and poorer control than in LTRA-treated children.

Introduction

International guidelines recommend inhaled corticosteroids (ICS) as preferred daily controller medication in children with asthma, with leukotriene receptor antagonists (LTRA) as alternative option[1–4]. These recommendations are based on solid evidence derived from randomized controlled trials showing

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greater efficacy of low-dose ICS monotherapy over LTRA[5–8]. These trials entailed rigorous drug prescribing and closely monitored subjects, resulting in higher drug use than typically observed in clinical practice. In contrast, drug claims generally reveal lower dispensing of ICS than LTRA with similar or better health outcomes with LTRA than ICS, raising some uncertainty as to the relative effectiveness of ICS versus LTRA in real-life practice[9,10].

Pharmacoepidemiological studies using administrative health databases are a powerful means of assessing drug use and health impact in clinical practice but are subject to several biases. Merging with individual patient medical records reduces these limitations; it provides patient characteristics which can assess the magnitude and direction of biases and prescribing details which can identify controller medications prescribed for intermittent, rather than maintenance, use and to assess the quality of prescription. Although low drug claims are frequently attributed to inadequate patient compliance, suboptimal physician prescribing has recently emerged as a distinct contributor[11,12].

The objective of this study was to examine the relative effectiveness of LTRA versus ICS as monotherapy on health outcomes of children with mild or moderate asthma, using information obtained from merged administrative health databases and individual patient data including prescription patterns, pharmacy dispensing, and possession of asthma controllers.

Patients and methods

Study design

We accrued a retrospective cohort of children who presented to the Asthma Center of a tertiary care pediatric hospital. The protocol was approved by the institutional review boards of CHU Sainte-Justine and Montreal Children's Hospital. Permission to access medical records without patient consent and link them to governmental administrative databases was granted by the Director of Professional services and the Commission d'accès à l'information du Québec.

Data sources

The electronic Asthma Center database recorded patient demographics; asthma phenotype, severity and control[13]; lung function, when applicable; drugs prescribed for maintenance use and step-up therapy during exacerbations; guided self-management and monitoring; and, for initial visits, co-morbidities and environmental triggers. Asthma phenotype was based on the absence (episodic) or presence of symptoms between episodes (persistent) and occurrence of symptoms solely during specific allergic seasons (seasonal)[1,3,14]. Severity was assessed by the intensity of treatment required to maintain disease control, with mild asthma well-controlled on LTRA or low doses ICS ($\leq$200 μg/day of HFA-BDP_{eq}) and moderate asthma requiring more than 200 μg but less than 400 μg/day of HFA-BDP_{eq} to achieve control (or partially controlled on LTRA or lower ICS doses)[1]. Having two or more recognized triggers was considered multi-trigger asthma[15–17]. Asthma control was examined by: spirometry (Masterscreen, Jaeger GmH, Wartzberg, Germany) before and after bronchodilation with 400 μg albuterol in cooperative children[18]; the 6-item Asthma Quiz for Kidz score[13]; and/or the physician global assessment of control. Asthma Center physicians were pediatric specialists with certification in pediatrics, allergy and immunology, or respirology. The database was linked to the Asthma Education Center database and the Emergency Department database, both logging visit dates and diagnosis. These hospital databases were merged with three provincial administrative health databases namely: (1) MED-ECHO database of all acute care hospital admissions, coded in the International Classification of Diseases (ICD) 9th version until 2006 and 10th revision, thereafter; (2) Régie de l'assurance-maladie du Québec (RAMQ) Prescription Drug Insurance database, providing dates of coverage, drug name, form, and strength, duration, quantity prescribed, and dispensation date of all prescriptions filled by insured Quebec residents; insured residents representing 42% of the population who obtain free prescription drugs for their children; and (3) RAMQ Medical Services database with the date and site of medical visits, ICD-9 diagnostic codes, and physician's specialty. Canadian residents are covered by universal healthcare with medical services provided free of charge.

Subjects

Patients were eligible if they: were aged 2–17 years, presented to the Asthma Center between January 2000 and December 2007, received a diagnosis of asthma of mild or moderate severity by an Asthma Center physician, were prescribed as controller monotherapy either LTRA or a low or medium dose of maintenance inhaled corticosteroids (ICS) ($\leq$250 μg/day of hydrofluoroalkane-propelled beclomethasone or equivalent [HFA-BDP_{eq}]), and were covered by the Quebec medical and drug plans. Children with other chronic lung diseases were excluded. The date at which the patient filled all inclusion criteria constituted the index date. The end date represented the date of the last Asthma Center visit, the end of coverage by the Quebec medical and drug plans, or December 31, 2007, whichever occurred first.

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Outcomes and determinants

The primary outcome was the rate of rescue oral corticosteroids dispensed by pharmacies per person-year, excluding those for which the available diagnostic code was not asthma (e.g., dermatitis). Secondary outcomes included acute-care visits defined as an emergency department visit (or a clinic visit with repeated examinations on the same day) with asthma as diagnostic code; hospital admissions with asthma as primary or secondary diagnosis; and weekly use of four or more doses of short-acting β_2-agonist, computed as the cumulative number of doses of all preparations dispensed divided by the length of follow-up. The proportion of prescription duration, also called the 'Proportion of Days with Supply Prescribed (PDSP),' represented the summed duration in days of all available prescriptions (new and permitted refills) received by pharmacists, divided by days of follow-up[19]. The proportion of prescribed days covered (PPDC), a marker of patient compliance, was calculated as the number of days for which the drug was dispensed, divided by the number of days for which it was prescribed[19]. The proportion of days covered (PDC), indicative of drug possession, was computed as the cumulative number of days for which the prescribed drug was dispensed divided by days of follow-up[20].

Statistical analysis

We estimated that 500 children would provide 80% power to detect a rate ratio of 1.7 at a two-sided alpha of 5%, assuming a baseline rate of rescue oral corticosteroids of 0.2 course per person-year[5]. Recognizing group imbalances in baseline characteristics prior to any outcome analysis, children were matched on age, gender and number of acute-care asthma visits in the preceding year; these variables were chosen because of completeness data on healthcare services utilization for all children, in contrast to rescue drug use (i.e., β_2-agonists or oral steroids) available only for patients with uninterrupted public drug coverage in the preceding 12 months. We used the greedy matching algorithm (GMATCH macro, SAS) in a 3:1 (ICS to LTR) ratio, allowing all LTRA-treated children to be included while maximizing the number of corresponding ICS-treated children. The date at which a child met the inclusion criteria was deemed the index date. We analyzed by intention-to-treat, all children from index- to end-date, irrespective of therapy discontinuation, step-up, or cross-over during follow-up.

We analyzed data using generalized linear regression models with normal, binomial, or Poisson (with overdispersion) distribution, depending on the outcome. When applicable, an offset was used to account for varying person-time; analyses were adjusted for length of follow-up and baseline values of the outcome under study. Two or more identical events (oral corticosteroids, acute care visit or admission) occurring within 7 days were counted once, assuming they pertained to the same exacerbation. Seasonal rates of dispensed medications, using claims as unit of analysis, were modeled for ICS and LTRA, adjusting for between-season correlation within calendar year, with the log of the number of patients covered by the drug plan as offset variable. Crude estimates were adjusted for group imbalances and potential confounding variables (age, gender, neighborhood financial income using 6-digit postal codes as a surrogate[21], phenotype, asthma control variables, physician specialty, written action plan, symptom diary, asthma education, continuity-of-care, and calendar year) using backward regression models. The continuity-of-care index reflected the extent to which a child saw the same physician during the observation period, with one indicating that all visits were with the same physician[22]. *P*-values less than 0.05 indicated statistical significance, with no correction for multiple testing. Analyses were performed using SAS software (version 9.2, SAS Institute Inc., Cary, NC, USA).

Results

Of the 14,950 visits logged in the Asthma Center database, 2095 visits were ineligible and 3431 (87%) children were excluded, mainly because of no prescribed maintenance monotherapy (60%) or no provincial drug plan (28%) Figure E1. The 530 eligible children were matched in a 1:3 ratio, resulting in the exclusion of 303 ICS-treated children; those not retained were significantly younger (mean age: 5 vs. 8 years, $p<0.0001$), more likely to have episodic asthma (41 vs. 27%, $p=0.0002$), moderate asthma (31 vs. 23%, $p=0.05$), and at least one acute-care visit in the previous year (61 vs. 24%, $p<0.0001$) compared to selected children. The cohort consisted of 227 children, 58 prescribed LTRA (montelukast) and 169 prescribed ICS at a median starting dose of 250 (range 200–250) µg/day of HFA-BDP$_{eq}$.

Baseline group characteristics were comparable in most respects with the following exceptions, children treated with montelukast were more likely to have intermittent symptoms, less FEV_1 reversibility post-bronchodilation, better asthma control as per the physician global assessment, and less likely to receive written action plans and symptom diaries than those prescribed ICS (Table 1). In both groups, two-thirds of children were recommended to step-up therapy with ICS during flare-ups. The distribution of triggers was similar between groups, with 60% or more meeting the definition of multi-trigger asthma and less than 20% reporting only viral-induced triggers[15–17]. The phenotype was not stable over time as many children, originally labeled with episodic asthma, evolved towards a persistent phenotype, and vice versa (data not shown);

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Table 1. Characteristics of participants*.

	Inhaled corticosteroids		Montelukast		*p*-value
	N	*n* (%)	*N*	*n* (%)	
Demographics					
Age – years	169	8.6 (4, 12)	58	8.6 (4, 12)	0.83
Male sex	169	97 (57%)	58	33 (57%)	0.95
Race or ethnic group	160		53		
White		100 (63%)		40 (76%)	0.22
Black		17 (11%)		4 (8%)	
Other		43 (27%)		9 (17%)	
Neighborhood income – quintiles (Q)†	167		55		
Q1 – lowest		70 (42%)		16 (29%)	0.35
Q2		42 (25%)		16 (29%)	
Q3		22 (13%)		6 (11%)	
Q4		18 (11%)		9 (16%)	
Q5 – highest		15 (9%)		8 (15%)	
Asthma morbidity in the preceding year					
Patients with $\geq$4 doses of β_2-agonists/week	166	65 (39%)	56	21 (38%)	0.83
Patients with $\geq$1 courses of oral steroids	134	44 (33%)	46	13 (28%)	0.56
Patients with	169		58		
0 acute care visit for asthma		128 (76%)		44 (76%)	
1 acute care visit for asthma		25 (15%)		9 (16%)	0.98
$\geq$2 acute care visits for asthma		16 (10%)		5 (9%)	
Patients with $\geq$1 hospital admissions	169	16 (10%)	58	2 (3%)	0.14
Asthma assessment at index visit					
Asthma phenotype	169		58		
Episodic		45 (27%)		29 (50%)	0.001
Persistent or exclusively seasonal‡		124 (73%)		29 (50%)	
Asthma severity	169		58		
Mild		130 (77%)		50 (86%)	0.13
Moderate		39 (23%)		8 (14%)	
Asthma triggers	169		58		
Viral		130 (77%)		42 (72%)	0.49
Allergic		59 (35%)		21 (36%)	0.86
Effort		96 (57%)		31 (54%)	0.66
Weather		33 (20%)		13 (22%)	0.64
Others		5 (3%)		2 (3%)	0.85
Co-morbidities∫	132		44		
Allergic rhinitis		48 (36%)		15 (34%)	0.79
Forced expiratory volume in 1 second¶					
% predicted pre-bronchodilator value	101	94 (83, 104)	32	99 (91, 108)	0.08
% change post-bronchodilation	79	7 (3, 12)	23	4 (3, 8)	0.03
Asthma Quiz for Kidz score§	57	2 (0, 3)	22	1 (0, 2)	0.10
Physician global assessment of control	130		36		
Good		45 (35%)		22 (61%)	
Satisfactory		62 (48%)		13 (36%)	0.007
Poor		23 (18%)		1 (3%)	
Guided self-management	169		58		
Asthma education		26 (15%)		6 (10%)	0.34
Written action plan		65 (39%)		6 (10%)	<0.0001
Home management of deterioration	169		58		
Inhaled corticosteroids step-up§§		113 (67%)		37 (64%)	0.67
Oral steroids		1 (1%)		0 (0%)	—
Symptom-based diary	169	58 (34%)	58	9 (16%)	0.007
Physician specialty	169		58		
Allergist		35 (21%)		13 (22%)	
Pulmonologist		7 (4%)		3 (5%)	0.90
Pediatrician		127 (75%)		42 (72%)	

*Values are reported as median (25%, 75%) or *n* (%).

†Quintiles derived the Canadian 2001 census tract data by postal codes, with the province of Quebec serving as reference; 1 represents the lowest income quintile and 5, the highest[21].

‡As seasonal asthma was recorded in only 2 patients in the ICS group and none in the montelukast group, this phenotype was subsequently combined with that of persistent asthma. Of interest, when phenotype was based on the type of triggers, 64% and 60% has multi-trigger asthma in the inhaled corticosteroids and the montelukast groups, respectively.

∫Co-morbidities were documented only at the initial consultation to the Asthma Centre; missing patients are those for whom the index visit was not an initial visit.

¶Spirometry was obtained in cooperative children, pre- and post-bronchodilation, unless the child had taken inhaled ß$_2$-agonist or had a methacholine provocation in the previous 6 hours.

§A validated self-assessment measure of asthma control on a score of 0 (best) to 6 (worst), based on the number of indicators of poor control; this was documented from August 2004[13].

∫∫Global assessment of control was systematically obtained only in children with persistent (or seasonal) asthma; it was not mandatory in those with episodic asthma.

§§Step-up inhaled corticosteroids at the onset of a deterioration for children on maintenance inhaled corticosteroids or ICS treatment initiation for children on daily montelukast.

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yet at endpoint, there still remains more children with persistent asthma in the ICS- than in the montelukast-treated group. There was no significant group difference in follow-up duration, number of visits, and continuity-of-care index (Table E1).

Health outcomes and rescue medications

Twenty-one percent (21%) of children treated with ICS used rescue oral corticosteroids compared to 17% for LTRA, with no significant group difference per person-year (adjusted rate ratio [RR]: 1.10, 95% CI: 0.66, 1.84) (Figure 1A). The ICS group experienced more than a three-fold higher rate of hospital admissions and used more weekly doses of inhaled β_2-agonist compared to the montelukast group (5.72 vs. 3.42 doses) (Figure 1B).

Prescription and adherence patterns

Physicians prescribed montelukast in sufficient amount to cover 97% of the follow-up period, as opposed to 62% for ICS (Table 2). Children retrieved enough medication to cover 51% of the prescribed ICS days, compared to 74% for montelukast. Of interest, 14% and 22% of patients prescribed ICS and montelukast, respectively, never filled a single prescription of controller (RR: 0.63, 95% CI: 0.35, 1.16); when these were included, the drug dispensed allowed ICS use over a median of 24% of follow-up, compared to 38% for LTRA. ICS claims were dispensed in a marked seasonal pattern, with a recurring summer drop and higher claim rates in the fall, winter, and spring; montelukast servings displayed no significant seasonal change (Figure 2). There was no group difference in the proportion of patients (3%) who switched to the alternate monotherapy. In 20% of ICS-treated patients, step-up of controller was prescribed compared to 5% in those on LTRA (RR = 4.18, 95% CI: 2.22, 7.86).

Discussion

In this cohort of children with mild and moderate asthma treated by pediatric asthma specialists, ICS use was not associated with a reduction in rescue oral corticosteroids

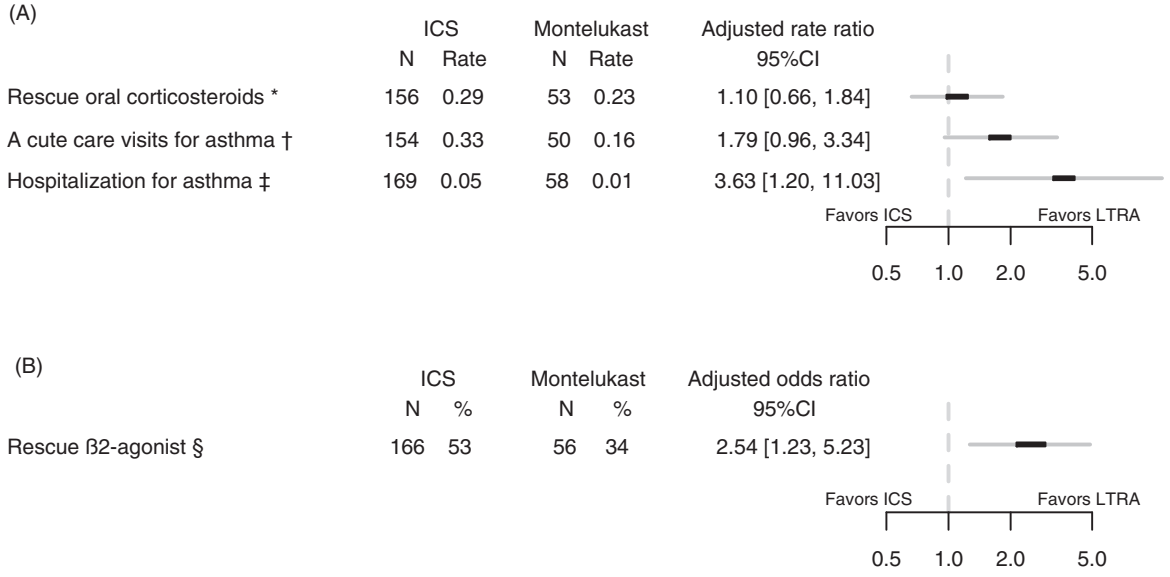

Figure 1. The group rates for inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) are displayed per person-year in (A) and as proportions in (B). All summary estimates were analyzed by intention-to-treat with adjustment for covariate. In (A), rate ratios are derived from Poisson regression (with over-dispersion) and an offset was used to account for varying person-time.

*Defined as a course of oral corticosteroids recorded by drug plan and for which the matching emergency visit or admission was coded for asthma; the rate ratio was adjusted for asthma severity, number of acute-care visits or rescue oral corticosteroids for asthma in the year preceding the index date, and the continuity-of-care index.

†Defined as an emergency department visit or a medical visit with repeat billings in the same day, both coded for asthma; the rate ratio was adjusted for financial income, allergic and weather inductions, cough, inhaled corticosteroid step-up or initiation during exacerbations, number of acute-care visits or oral corticosteroids for asthma in the year preceding the index date, and the continuity-of-care index.

‡Defined as a hospital admission in which asthma was the first or the second diagnosis when, for the later, the main diagnosis was a known asthma complication (such as atelectasis) or co-morbidity (such as pneumonia); the rate ratio was adjusted for number of acute-care visits or oral corticosteroids for asthma in the year preceding the index date.

§Defined as the proportion of children in whom the mean dose of short-acting β_2-agonist (assuming uniform intake) over the follow-up period exceeding four or more doses per week, where one dose refers to two inhalations of 100 μg albuterol or fenoterol, one inhalation of 0.5 mg terbutaline, or one nebule of β_2-agonist irrespective of dosage; the odds ratio was adjusted for length of follow-up and no. of short-acting β_2-agonist doses per week in the year before the index date.

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Table 2. Prescription and adherence patterns.

	Inhaled corticosteroids ($n=146$)	Montelukast ($n=45$)	Adjusted mean group difference (95% confidence interval)
Proportion of follow-up days for which a supply of controller medication was prescribed (PDSP)*	62% (35%, 99%)	97% (43%, 100%)	–17.06 (–27.52, –6.60)
Proportion of prescribed days for which patient obtained controller medication from pharmacy (PPDC)†	51% (34%, 71%)	74% (48%, 86%)	–12.00 (–20.15, –3.86)
Proportion of follow-up days for which patient obtained controller medication from pharmacy (PDC)‡	27% (14%, 45%)	52% (28%, 75%)	–19.39 (–27.52, –11.26)
Proportion of follow-up days for which patient obtained medication from pharmacy, including patients who never filled a controller prescription§	24% (10%, 39%)	38% (6%, 74%)	–14.21 (–22.29, –6.12)

All values are displayed as median (25%, 75%).

*This parameter is a marker of physician prescribing: it reflects the duration of all prescriptions available at pharmacies that are available to be served to the patient during the follow-up period. The prescription duration was calculated by pharmacists assuming that patients took the medication as prescribed; it is also known as the 'Proportion of follow-up Days for which Supply was Prescribed (PDSP).'[18] The group mean difference was adjusted for asthma phenotype and viral induction.

†This parameter is a marker of patient adherence; it reflects the period covered by the prescribed drug dispensed by pharmacies. It is also known as the 'Proportion of Prescribed Days Covered (PPDC);'[18] the mean group difference was adjusted for age at the index visit and physician specialty.

‡An indicator of overall usage, this parameter is also known as the 'Proportion of Days Covered (PDC) by a prescription served by pharmacies[18,19];' the mean group difference was adjusted for viral induction.

§An indicator of overall usage, but taking into account the 14% of patients in the ICS and 22% in LTRA groups who never brought to any pharmacy a single prescription of controller medication during the follow-up period; the mean group difference was adjusted for asthma phenotype, length of follow-up, and viral induction.

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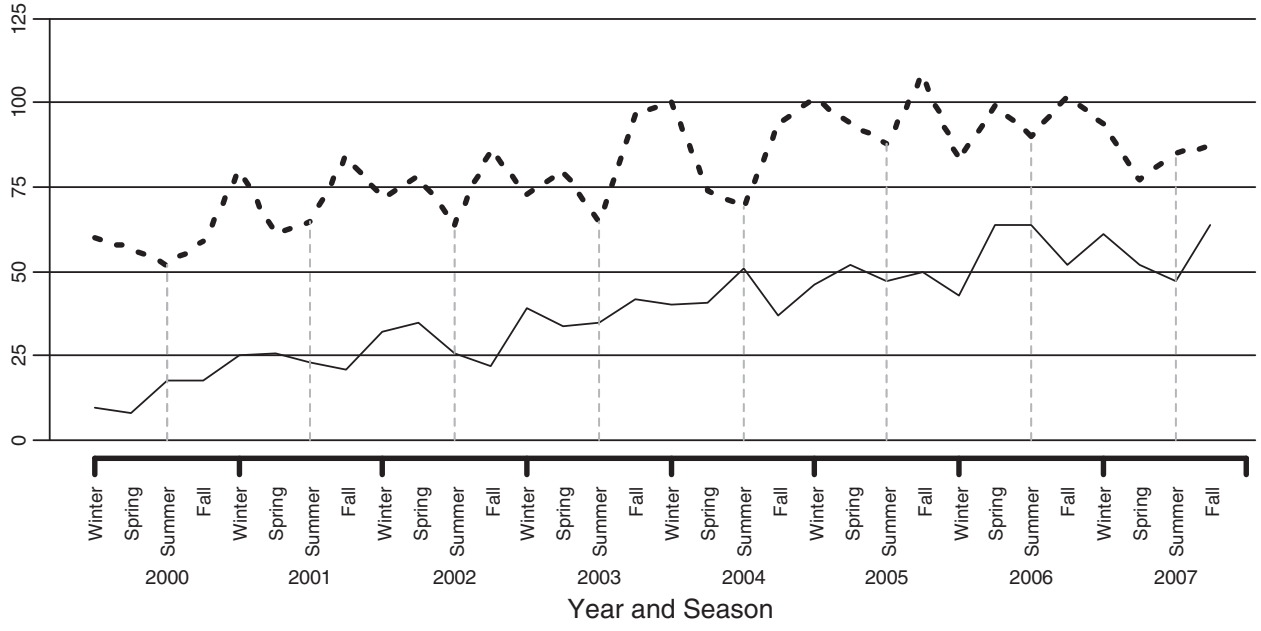

Figure 2. The pharmacy dispensing of inhaled corticosteroids (ICS: dark dotted line) and leukotriene receptor antagonists (LTRA: light full line) are depicted by season and year, throughout the observation period. A seasonal pattern was evident for ICS with a drop in the rate of claims/person-season in the summer (0.43, 95% CI: 0.40, 0.47) compared to the fall (0.53, rate ratio: 1.23, 95% CI 1.14, 1.33), winter (0.48, rate ratio: 1.10, 95% CI 1.01, 1.20), and spring (0.47, rate ratio: 1.08, 95% CI 1.00, 1.16); a seasonal pattern was not observed for montelukast with rates/season-year of 0.23 (95% CI 0.19, 0.29) for the fall, spring and summer and of 0.21 (0.17, 0.26) in the winter. There is an upward secular trend with an increase in claims for both controllers over time.

and acute-care visits for asthma; instead ICS-treated children experienced a three-fold increase in hospital admissions and more fast-acting β_2-agonist use than montelukast-treated group. Although the lower than expected effectiveness of ICS could be explained by a slightly greater disease activity on baseline, paradoxically, physicians prescribed significantly less drug supply of ICS than montelukast ($p<0.0001$) and patients obtained less ICS than LTRA from available prescriptions ($p<0.05$). The contribution of the physician prescription pattern to both low and differential drug claims, while confirming recent findings[11], raises important questions on obstacles

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to optimal long-term controller prescribing by pediatric specialists.

In line with prior observational reports, we observed no group difference in the rate of rescue oral corticosteroids, our primary outcome[10,23]; the matching process reduce baseline group differences but also affected power. However, the threefold increase in asthma hospitalization rate, the two-fold higher odds of β_2-agonists overuse, and the trend towards a two-fold increase in acute-care visits persisting despite statistical adjustment highlighted the poorer asthma control in ICS- compared to the montelukast-treated group. These findings contrast with a Cochrane review showing that patients taking LTRA experienced a 65% higher risk of exacerbations requiring oral corticosteroids than those on low-dose ICS[5]. Two main hypotheses may explain the discordant findings. First, despite matching and statistical adjustment, children prescribed montelukast appeared to have slightly better asthma control at baseline than those treated with ICS, suggesting residual confounding by indication, where, in line with guideline recommendations, ICS are preferred over LTRA. Secondly, most published trials showing superiority of ICS over LTRA were efficacy studies[5,8,24], in which treatment protocols were administered with high adherence. In contrast, in this effectiveness study, children on ICS claimed significantly less medication – enough to barely cover a quarter of the follow-up period – compared to a third for montelukast ($p = 0.007$); both considerably suboptimal. Moreover, the profile of ICS dispensing bore close resemblance to *summer drug holidays*[25,26], whereas montelukast, rising as the drug permeated the market, showed no significant seasonal variation. The marked suboptimal, and differential, possession rate of both monotherapies is in line with prior reports favoring longer persistence of LTRA over ICS[9–11,23], and suggest that lower ICS persistence is contributing, at least in part, to the dilution of ICS efficacy. This is particularly bothersome in view of the slightly higher baseline disease activity in ICS- than LTRA-treated patients.

A substantial proportion of families never brought a single prescription of controller to pharmacies over the observation period. Similar findings were observed by Butz and colleagues[27] for ICS-treated adults; to our knowledge, no such report is available for montelukast in adults or children. Patient adherence to filling prescriptions of asthma controllers is notoriously low, barely approaching 50% of prescribed ICS[9,28], in line with our observations. The differential claim rate favoring LTRA over ICS is consistent with several reports[9–11,27]. Consistent with less severe asthma and despite similar rate of step-up therapy during exacerbations, fewer montelukast- than ICS-treated children received written action plans or were requested by their physicians to complete asthma symptom diaries. As written action plans have been shown to increase drug adherence[29], the higher drug compliance with montelukast than ICS in children with fewer action plans, suggest a different explanation. Fear of ICS side-effects[30], faster resolution of symptoms in ICS-treated patients who endorsed the erroneous concept that no symptoms equate no disease[31], and preference of a once-daily tablet over inhalers may explain a higher drug claim for montelukast.

Novel indices developed by Blais and colleagues allowed the distinction between physician- and patient-related causes of low medication possession[12]. The prescribed ICS dispensed covered 62% of the follow-up period, a period 17% shorter than that of montelukast. Our findings are in line with, albeit less impressive than, the 40% shorter period covered by available ICS, compared to LTRA, prescriptions in our previous cohort of 27,355 children[11]. While in the former study, we conjectured that the shorter period may be due to ICS prescribed as intermittent therapy[11], in this cohort, physicians prescribed controllers as daily maintenance in all patients, as we specifically excluded 60% of children treated with intermittent controller therapy. Why then the shorter ICS prescription duration compared to LTRA? Most studies on physician prescribing have concentrated on the appropriateness of prescription[32], few on prescription duration of asthma controllers[9,11]. Physician specialty[23,33,34] and patient ability to pay[35] are unlikely to have influenced prescription patterns as all physicians were asthma specialists and all patients had access to free medication; physician specialty and patient neighborhood financial income were not predictors of prescription duration. Perhaps physicians prescribed shorter supplies of ICS than LTRA because of guidelines' imprecision about duration of daily therapy including summer holidays, more rapid resolution of symptoms, concern about side-effects or as a strategy to ensure timely medical follow-up[25,30,34]. Clearly, while pediatric specialists and subspecialists generally prescribe better than general practitioners, their adherence to guidelines remain suboptimal[30,34].

The findings must be interpreted in light of the following strengths and limitations. Our ability to link detailed clinical health records with medication claims and healthcare utilization provided key advantages to assess the quality of prescribing, including the assurance that controllers were prescribed for maintenance, not intermittent, use, quantification of prescriptions never reaching pharmacies, and adjustment of health outcomes for patient characteristics. Pediatric specialist-diagnosed asthma represented a significant advantage over diagnosis inferred from drug claims or diagnostic codes. However, the lack of randomization led to group imbalances in size – which decreased power – and in baseline characteristics; while the latter improved with matching and statistical adjustment, we could not rule out residual confounding by indication. The inclusion of 27–50% children with *episodic* asthma, in whom use of maintenance therapy may not be indicated,

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may be debatable[36]. As with other studies[27], patient selection was based on prescribed daily controllers as a marker for persistent asthma, rather than the reported phenotype itself, because *persistent* may refer to long-term prognosis[37], presence of interim symptoms, or multi-trigger asthma[15,17], resulting in substantial between-physician and within-patient variability. The large number of children with multiple triggers supported our decision. Drug dispensing does not ensure actual usage; however, usage cannot happen without dispensing. Although we did not document the provision of samples, they were usually offered to children with private drug insurance, rather than those for whom the medications were free. Finally, the small sample size prevented us to explore patient and physician characteristics associated with prescription pattern and adherence behavior.

The results of this study apply primarily to school-aged children, benefiting from a universal health insurance with free drug plan, treated by pediatric specialists in a tertiary-care asthma center. Thus, the suboptimal prescribing and drug dispensing likely overestimate that observed in the community or in settings where drugs must be purchased. Although the similarity of our findings with adherence reports in children and adults[38], in both insured[23] and underserved[27] populations in the US, adds credibility to our findings, replication in other settings is warranted.

Conclusions

The lower ICS than LTRA drug dispensing in a population of children with slightly poorer asthma control on baseline is paradoxical and raises concern. The differential and lower duration of ICS prescriptions by physicians and lower ICS claims by patients compared to LTRA likely diluted the expected efficacy of ICS. The findings underline the importance of effectiveness studies when evaluating obstacles to implementation of guidelines recommendations. One should not refrain from prescribing ICS but pay attention to prescribe enough supply for long-term intake, including during the summer to curtail the September asthma epidemic. As controller use clearly appears more important than potency to maintain asthma control, attitudes, beliefs and behaviors affecting long-term controller prescribing by physicians – and intake by patients – must be explored.

Transparency

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