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Should we Substitute Intermittent for Maintenance Inhaled Corticosteroids in Patients with Persistent Asthma? A Systematic Review and Meta-Analysis

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Abstract

Background: Although guidelines recommend maintenance inhaled corticosteroids (ICS) in mild persistent asthma, most patients use, and many physicians prescribe, intermittent ICS.

Objective: To compare the efficacy and safety of maintenance versus intermittent ICS in children and adults with persistent asthma and to explore potential effect modifiers attributable to either strategy.

Methods: We searched the literature using: the Cochrane airways group specialized register of trials and ClinicalTrials.gov website until October 2012. All randomized controlled trials, at least of four-week duration, comparing maintenance and intermittent ICS initiated at the onset of exacerbations. The primary efficacy and safety outcomes were the risk of patients with exacerbations requiring rescue oral corticosteroids and serious adverse events, respectively. Secondary outcomes included exacerbations, asthma control, lung function, airway inflammation, withdrawals, and adverse events.

Results: Six (4 pediatric; 2 adult) trials involving 1211 patients with mild persistent asthma met the eligibility criteria; they lasted 12-52 weeks. There was no statistically significant group difference in the risk of patients with exacerbations requiring rescue oral corticosteroids (RR 1.07; 95% CI 0.87, 1.32). The response magnitude was not influenced by age, asthma severity, step-up protocol, and intervention duration. Maintenance ICS was superior to intermittent ICS in several indicators of symptoms, ß2-agonist use, lung function, and airway inflammation. There was no group difference in the risk of patients with serious adverse events (RR=0.82; 95% CI 0.33, 2.03). In children, maintenance ICS was associated with less linear growth (MD=0.41 95% CI 0.13, 0.69) over 44-52 weeks.

Conclusions: In children and adults with persistent asthma, maintenance and intermittent ICS strategies did not significantly differ in the risk of patients experiencing exacerbations requiring rescue oral corticosteroids and severe adverse events; however the wide confidence interval precludes equivalence. Maintenance ICS was superior to intermittent ICS in several indicators of lung function, airway inflammation, asthma control and reliever use. The paucity of trials prevents firm conclusions.

Keywords: Adults; Asthma; Children; Inhaled corticosteroids; Intermittent; Randomized controlled trial; Systematic review

Introduction

National and international asthma guidelines recommend maintenance inhaled corticosteroids (ICS) as the mainstay of treatment in children and adults with mild persistent asthma [1-4]. However, patients often discontinue their maintenance ICS treatment when asymptomatic and restart treatment when deemed required, that is, at the onset of exacerbations [5]. Poor adherence to ICS treatment appears to account for a significant proportion of asthma related emergency department visits and hospitalizations [6,7]. Moreover, many physicians prescribed intermittent, rather than maintenance, ICS to children [8] and adults [6,9] with persistent asthma.

In a landmark study, Boushey et al. tested intermittent ICS as an alternative to maintenance ICS in adults with mild persistent asthma; they concluded to the superiority of maintenance over intermittent ICS and that of intermittent ICS over placebo [10]. The concept of intermittent ICS as a viable alternative to maintenance ICS has been subsequently explored in several trials in preschoolers [11,12], school-aged children [13,14], and adults [10,15] with persistent asthma.

The objectives of the review were to compare the efficacy and safety of maintenance ICS versus intermittent ICS in the management of children and adults with persistent asthma. We also wished to identify the characteristics of patients and treatment more likely to be associated with a satisfactory response to either treatment strategy. The detailed review and its 2013 update is available in the Cochrane Database of Systematic Reviews (DOI: 10.1002/14651858.CD009611) [16,17].

Methods

Search strategy and data extraction

The literature search was conducted in the Cochrane Airways

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Group Specialized Register of trials (Appendix) [17]. We also conducted a search of ClinicalTrials.gov web site using "intermittent" as keyword, "asthma" as condition and "interventional studies" as study type. All databases were searched from their inception until October 2012, with no language constraints.

All citations that were clearly not randomized controlled trials or did not fit the inclusion criteria were excluded. The full-text articles for all potentially eligible trials were obtained and independently assessed for inclusion by two authors. Only randomized controlled trials comparing maintenance ICS to intermittent ICS over a minimum of four weeks in children and adults with persistent asthma and preschoolers with suspected persistent asthma were included. No additional anti-asthmatic drugs were permitted, other than rescue short acting β2-agonists and oral corticosteroids. Eligible full text papers were independently reviewed by two authors for methodological quality and data extraction. Discordances were resolved by consensus or the input from a third reviewer.

Assessment of methodological quality

The methodological quality was evaluated using the Cochrane Risk of Bias tool [18], which assesses random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment, completeness of data reporting, selective reporting of outcomes and other bias. A trial was considered of high methodological quality if it met the following minimal criteria: convincing use of random sequence generation and double-blinding, and near-complete data reporting (i.e., a low and balanced withdrawal rate between groups). We contacted all authors to confirm the methodological quality and the accuracy of extracted data and to solicit additional unpublished data, if required.

Primary and secondary outcomes

The primary efficacy and safety outcomes were the risk of patients experiencing one or more exacerbations requiring rescue oral corticosteroids and of patients with serious adverse health events, respectively. In line with the latest Global Initiative for Asthma and the International consensus on pediatric asthma [1,19], secondary outcomes included: (1) indices of current clinical control (i.e., asthma control days, symptoms, rescue β_2-agonists use, quality of life, lung function, and airway inflammation) and (2) markers of future risk namely, the severity or frequency of exacerbations (i.e., exacerbations requiring an acute care visit, hospital admission, time to exacerbation requiring oral corticosteroids), withdrawals, and adverse health events.

Statistical analyses

Pooled treatment effects for dichotomous variables were calculated as risk ratio (RR) or odds ratio (OR) with 95% confidence interval (CI); we assumed equivalence if the summary estimates and its 95% CI were between 0.9 and 1.1. For continuous outcomes, we calculated pooled statistics as either mean difference (MD) or standardized mean difference (SMD) with 95% CI, as indicated. In trials reporting more than two groups of interest, we considered additional comparisons, if appropriate. To avoid over-representation when the control group served twice as comparator, we halved the number of participants for continuous outcomes and halved both the numerator and denominator for dichotomous outcomes. The homogeneity of outcomes between studies being meta-analysed was evaluated using both the Chi2 (χ^2) test for heterogeneity and the I^2 statistic; $P<0.10$ or an $I^2>40\%$, respectively were deemed indicative of significant heterogeneity [20]. In the presence of statistical heterogeneity, the DerSimonian & Laird random-effects model [21] was applied to the summary estimate; otherwise a fixed-effect model was used. Irrespective of heterogeneity, subgroup analyses were planned *a priori* to explore a potential effect modification of the following variables on primary efficacy and safety outcomes: age, baseline severity of airway obstruction, step-up protocol during exacerbations, and trial duration. Sensitivity analyses served to determine the impact of poor methodological quality, unpublished trials, and uncertainty regarding the persistent asthma phenotype, on the primary efficacy estimate. We performed the meta-analysis using Review Manager 5 (Cochrane Review Manager, Cochrane Collaboration, Oxford, UK) [22].

Results

Of 233 citations identified, 227 citations did not meet the inclusion criteria. Six parallel-group, randomized controlled trials (contributing seven comparisons) were eligible and contributed data to the meta-analysis (Figure 1). All trials were of high methodological quality (eTable 1), published in full-text, and funded by pharmaceutical companies. Trials enrolled school-aged children [13,14], and adults [10,15], with persistent asthma (i.e., documented interim symptoms) or preschoolers [11,12] with suspected persistent asthma (i.e., repeated wheezing, with or without interim symptoms or a positive asthma predictive index) [23] for a total of 1211 patients (498 preschoolers, 330 school-aged children and 383 adults) (Table 1). With the exception of the two preschool-aged trials, all studies enrolled individuals with symptomatic mild persistent asthma (although one paediatric trial admitted that, in retrospect, their participants probably had mild or moderate airway obstruction at baseline) [14]. Most trials described a gender ratio varying between 38% to 69% males. Two trials reported atopy in 36% to 61% of participants [11,13]. Participants were stepped down to placebo and as needed β_2-agonist in three comparisons [11,15], while the rest of the trials used anti-asthma treatments to meet inclusion criteria for the run-in period of two to four weeks. The patients using beclomethasone dipropionate or budesonide, included trials tested one of four strategies during exacerbations: a 4-fold ICS step-up in both groups or only in the intermittent group, the use of ICS whenever β_2-agonist was needed in both groups or only in the intermittent group. Trials varied in length between 12 and 52 weeks. No trial clearly documented the absence of interim symptoms and normal lung function (when feasible) on low dose maintenance ICS in all patients, before they were allocated

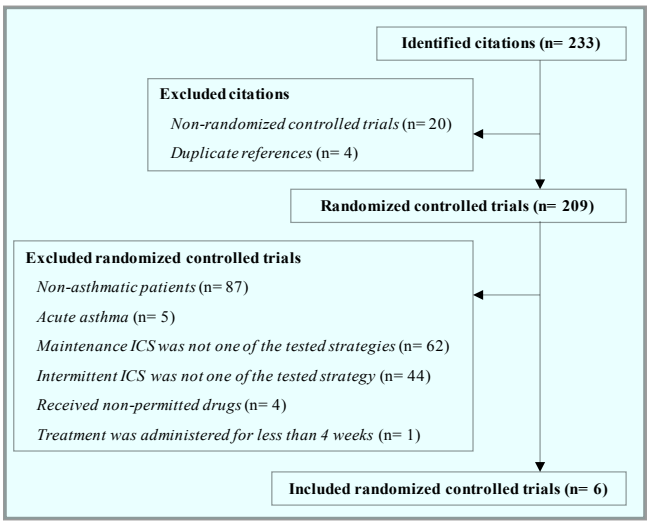

Figure 1: Selection of randomized controlled trials.

Trials	Random sequence generation	Allocation concealment	Blinding of participants, personnel and outcomes	Complete outcome data*	Selective outcome reporting†	Other bias
Turpeinen et al. [14]	+	±	+	+	+	+
Boushey et al. [10]	+	+	+	+	+	+
Zeiger et al. [12]	+	+	+	?	+	+
Martinez et al. [13]	+	+	+	+	+	+
Papi et al. [11]	+	+	+	+	+	+
Martinez et al. [13]	+	+	+	+	+	+
Papi et al. [15]	+	+	+	+	+	+

+=low risk of bias (high methodological quality); ? =insufficient information to permit a judgment regarding the risk of bias (despite contacting authors).
A trial was considered to be of high methodological quality if it convincingly used random sequence generation, double-blinding, and reported low and balanced withdrawal rate with complete reporting of outcomes [18].
*Complete outcomes data describes the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Whether attrition and exclusions were reported, the numbers in each intervention group, reasons for attrition/exclusions were reported, and any re-inclusion in analyses performed by the review authors.
†Selective outcome reporting involves checks for the possibility of selected outcome reporting or changing the primary outcome.

eTable 1: Methodological quality of included trials determined using the Cochrane Risk of Bias tool [18].

Trials	N	Age (yrs)	% Predicted FEV_1	Between exacerbations*	During exacerbations†		Duration (Weeks)
				Maintenance ICS	Maintenance ICS	Intermittent ICS	
4-fold ICS step-up in both groups							
Turpeinen et al. [14]	116	7	77%	BUD 200 µg/day	BUD 800 µg/day	BUD 800 µg/day	52
Boushey et al. [10]	149	33	89%	BUD 400 µg/day	BUD 1600 µg/day	BUD 1600 µg/day	52
4-fold ICS step-up only in intermittent group							
Zeiger et al. [12]	278	NR§	NR	BUD 500 µg/day	BUD 500 µg/day	BUD 2000 µg/day	52
ICS+β_2-agonist in both groups‡							
Martinez et al. [13]	143	11	101%	BDP 100 µg/day	BDP 100 µg/day+BDP 100 µg and rescue albuterol prn	BDP 100 µg and rescue albuterol prn	44
ICS+β_2-agonist in the intermittent group only‡							
Papi et al. [11]	220	2	NR	BDP 800 µg/day	BDP 800 µg/day	BDP 800 µg and salbutamol 1600 µg nebule prn	12
Martinez et al. [13]	71	11	102%	BDP 100 µg/day	BDP 100 µg/day	BDP 100 µg and rescue albuterol prn	44
Papi et al. [15]	234	38	88%	BDP 500 µg/day	BDP 500 µg/day	BDP 500 µg/day and albuterol 100 µg prn	24

N=Number of patients in treatment groups of interest; FEV_1=Forced expired volume in one second; BDP=Beclomethasone dipropionate; BUD=Budesonide; NR=Not reported.
*Maintenance corticosteroids were inhaled [10,13-15] or nebulized [11,12]
†All trials recommended the use of rescue β_2-agonist as-needed. All trials tested one of four strategies during exacerbations: a 4-fold ICS step-up in both groups [10,14] or only in the intermittent group [12], the use of ICS whenever β_2-agonist was needed in both groups [13] or only in the intermittent group [11,13,15]. ICS and β_2-agonist could be administered in separate inhalers [13], in the same inhaler [15] or separate [12] or same [11] nebule.
§Age was reported as 12 to 52 months.

Table 1: Characteristics of included trials.

to intermittent or maintenance ICS; in such as a case, intermittent therapy would have been considered as a step-down option. Rescue oral corticosteroids were physician-initiated after a medical consultation for an exacerbation in all, but one trial [10]; in the latter, patients were instructed to notify study personnel and self-initiate oral corticosteroid for five days upon meeting set criteria of an acute exacerbation.

There was no statistically significant group difference in the risk of patients experiencing one or more exacerbations requiring rescue oral corticosteroids (RR 1.07; 95% CI 0.87, 1.32) (Figure 2A), with no apparent statistical heterogeneity. The magnitude of effect was not influenced by patients' age (preschoolers versus school-aged children versus adults; χ^2 1.61, df 2, P 0.45), baseline severity (mild versus moderate airway obstruction; χ^2 0.81; df 1; P 0.37), ICS dose during exacerbation (χ^2 0.63, df 3, P 0.89), or trial duration (12-24 versus 44-52 weeks; χ^2 0.07, df 1, P 0.79). Similar results were observed after removing the data from the single trial [12] that included preschoolers on the basis of frequent wheezing episodes without interim symptoms (RR 1.13; 95% CI 0.80, 1.60) or both preschool-aged trials [11,12] contributing data to this outcome (RR 1.04; 95% CI 0.73, 1.49). Due to the homogeneity of trial design, no sensitivity analyses were done on methodological quality and publication status.

With regards to asthma control, the intermittent ICS group experienced significantly fewer asthma control days, more rescue β_2-agonists use, less improvement in morning peak expiratory flow rate, greater increase in exhaled nitric oxide, and less reduction in symptom-free days compared to maintenance ICS; there was no statistically significant group difference in symptoms, quality of life and forced expiratory volume in one second (Table 2).

As for future risk, there was no statistically significant group difference in the risk of patients experiencing a serious adverse health event (RR 0.82; 95% CI 0.33, 2.03) (Figure 2B), with no heterogeneity across trials. The magnitude of effect was not influenced by patients' age (preschoolers versus school-aged children versus adults; χ^2 0.90, df 2, P 0.66), baseline severity (χ^2 0.84; df 1; P 0.36), or ICS step-up protocol during exacerbation (χ^2 1.08, df 3, P 0.78). Due to homogeneity of trials

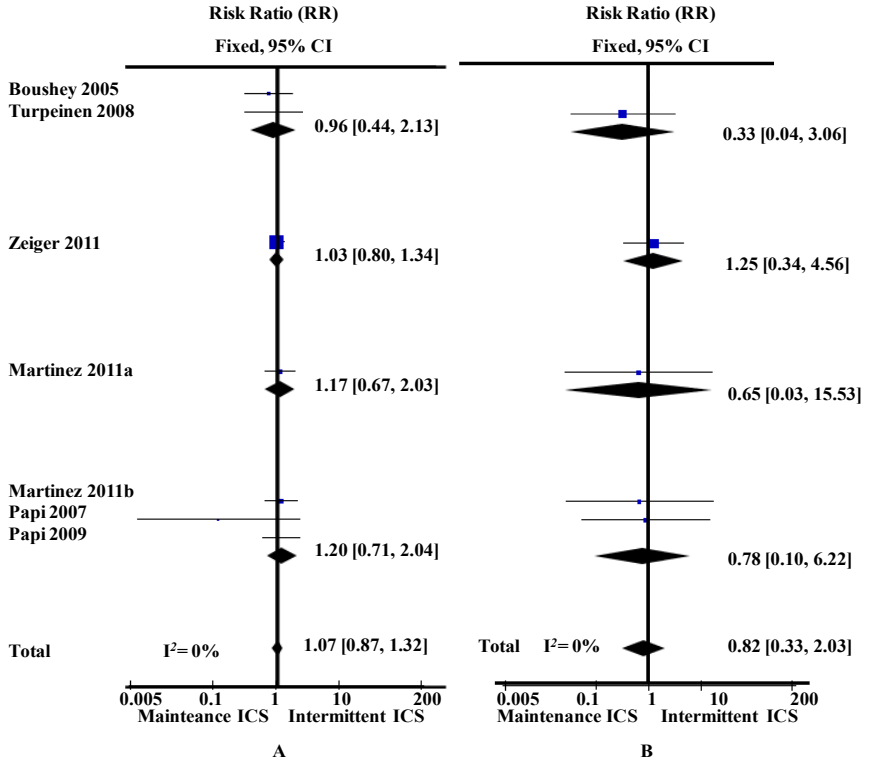

Figure 2: For each outcome, the risk of patients with one or more exacerbations requiring oral corticosteroids in A and of patients with serious adverse health events in B, one count per patient is counted. Each study is depicted by a point estimate represented by a square, the size of which corresponds to the weight of the study in the overall estimate represented by the diamond at the bottom of each graph. The error bars on either side of each square and the width of the diamond indicate the 95% confidence interval of the risk ratio (RR) estimates. The RRs are analyzed with the fixed-effect model and the heterogeneity across pooled trials is presented as I2. Summary estimates falling on the left side of the graphs favor maintenance ICS, those falling on the right side favor intermittent ICS.

contributing data, no subgroup analysis on duration of intervention was done.

There was no significant difference in the time to first exacerbation requiring oral corticosteroids, severity of exacerbations, withdrawals, overall or individual adverse effects; yet, the findings did not meet our *a priori* definition of equivalence. However, a significant difference was observed in the change from baseline in linear height at 44-52 weeks, in favor of intermittent versus maintenance ICS (Table 2).

Discussion

Based on four pediatric and two adult trials, our meta-analysis did not identify a significant group difference in the risk of patients experiencing one or more exacerbations requiring oral corticosteroids; yet, the large confidence interval precludes equivalence between maintenance and intermittent ICS. There was no statistically significant group difference in other markers of future risk namely, the severity of exacerbations, withdrawals, or serious adverse health events. Although all statistically significant, the magnitude of benefit of maintenance over intermittent ICS was clinically more important on asthma control (7% greater increase in asthma control days and 9% greater increase in symptom-free days) than on lung function and rescue β_2-agonist use. These benefits were observed at the cost of small, but significant, growth suppression in children receiving maintenance, instead of intermittent, inhaled beclomethasone dipropionate or budesonide.

Although most patients met the criteria of mild persistent asthma, the risk of experiencing an exacerbation requiring rescue oral corticosteroids was relatively high (18% and 19% in intermittent ICS and maintenance ICS groups, respectively), underlying ongoing disease activity. While the absence of group difference in the risk of patients experiencing one or more exacerbations requiring rescue oral corticosteroids might suggest that intermittent ICS is as effective as maintenance ICS to curtail exacerbations, it cannot be viewed as indicative of equivalence in view of the wide confidence intervals. The rate of exacerbations may be reduced by as much as 17% or increased by as much as 32% with intermittent ICS compared to maintenance therapy.

A similar wide confidence interval precluded a firm conclusion supporting intermittent ICS therapy in a recent study on adults who well controlled on baseline, where maintenance ICS was adjusted either by their physicians, based on the National Heart, Lung, and Blood Institute guidelines or based on exhaled nitric oxide level, or by patients who self-adjusted their ICS dose [24]. This trial did not meet our eligibility criteria as over 40% of patients in both physician-adjusted therapy groups stopped maintenance ICS within 2 weeks of randomization. This latter finding may suggest that a significant proportion of adults well controlled on maintenance ICS may not need regular therapy to prevent exacerbation (or perhaps they actually are suffering from intermittent, not persistent, asthma). Due to the large confidence interval observed in our review, it is clearly premature to suggest that this conclusion would also apply to those with uncontrolled persistent asthma on low dose ICS.

In our review focused on patients who were symptomatic on

Outcomes	N	Summary estimate	95% CI
Current clinical control			
Change from baseline in asthma control days	214	MD=-0.07	-0.14, -0.01
Proportion of asthma control days	330	MD=-0.09	-0.14, -0.04
Change from baseline use of β2-agonists (puffs/day)	442	MD=0.12	0.00, 0.23
Cumulative doses of rescue albuterol (µg)	214	MD=51.47	11.36, 91.57
Change from baseline morning PEFR (%)	350	MD=-2.56	-4.49, -0.63
Change from baseline in FEV1 (%)	365	MD=-0.49	-5.82, 4.84
Change from baseline in exhaled NO (parts per billion)	214	MD=16.80	11.95, 21.64
Change from baseline in the proportion of symptom-free days	984	SMD=-0.15	-0.28, -0.03
Change from baseline in daytime symptom scores	591	SMD=0.13	-0.04, 0.29
Change from baseline in night-time awakenings	448	MD=-0.03	-0.08, 0.02
Change from baseline in quality of life	389	SMD=-0.16	-0.36, 0.04
Future risk			
Time to first exacerbation requiring oral corticosteroids	492	HR=0.88	0.55, 1.40
Patients with ≥1 exacerbation requiring an acute care visit	1055	RR=1.08	0.90, 1.30
Patients with ≥1 exacerbation requiring a hospital admission	1204	RR=0.85	0.29, 2.49
Number of exacerbations requiring ED visits	264	RR=0.69	0.14, 3.44
Overall withdrawals	1210	RR=1.04	0.79, 1.37
Withdrawals due to poor asthma control	1063	RR=1.60	0.56, 4.52
Withdrawals due to adverse effects	1063	RR=0.78	0.21, 2.92
Overall adverse effects	726	RR=1.00	0.89, 1.13
Nausea	393	RR=1.15	0.56, 2.35
Upper respiratory tract infection	393	RR=1.14	0.96, 1.35
Change in height (cm)	532	MD=0.41	0.13, 0.69

MD: Mean Difference; SMD: Standard Mean Difference; HR: Hazard Ratio; RR: Risk Ratio; PEFR: Peak Expiratory Flow Rate; FEV_1: Forced Expired Volume In One Second; NO: Nitric Oxide.

Table 2: Secondary outcomes.

maintenance ICS, age, and baseline severity of airway obstruction, use of a fixed or 'as needed' ICS protocol during exacerbations, and duration of intervention did not appear to significantly impact the magnitude of effect. Whether administered as 4-fold increase from the baseline maintenance ICS dose or whenever a dose of ICS was added whenever a dose of rescue β_2-agonists was needed, the ICS dose during exacerbations did not appear to influence the magnitude of effect. This observation supports the conclusion derived from a recent Cochrane review where a two- to four-fold ICS step-up (1000 to 2000 µg/day) at the onset of an exacerbation was not associated with a statistically significant reduction in the risk of exacerbation requiring oral corticosteroids in adults on maintenance ICS [25].

As expected for individuals with mild persistent symptoms, a clinically important and statistically significant improvement was observed favoring maintenance, over intermittent, ICS in symptom-free days, asthma control days, and exhaled nitric oxide. Although statistically significant, the improvement in lung function and rescue β_2-agonist use, both in favor of maintenance ICS, were more modest, perhaps due to the predominantly normal lung function and low use of rescue bronchodilator at baseline in enrolled patients. In view of the variability in patient characteristics and treatment protocols, the findings consistently supporting maintenance, over intermittent, ICS for maintaining asthma control, suggest robustness in the observed superiority of maintenance over intermittent ICS in asthma control.

As for the safety profile, the absence of statistically significant group difference in withdrawal rates and in overall or specific adverse effects must be interpreted with caution due to the large confidence intervals. Of note, adverse effects typically associated with maintenance ICS, such as osteopenia and adrenal suppression, were not systematically documented. A modest, yet statistically significant, growth suppression of 0.41 cm (95% CI 0.13, 0.69) was observed, with 100 to 200 µg/day of hydrofluoroalkane-propelled beclomethasone (or equivalent) over 44-52 weeks. The observed growth suppression was smaller than the previously reported values of 1.54 cm/year and 1.1 cm/year with 400 µg of maintenance inhaled beclomethasone and 200 µg of maintenance inhaled budesonide, respectively [26,27]. The lower than expected group difference between maintenance and intermittent ICS may be due to the documented growth suppressing effect of intermittent high dose ICS itself, as previously noted by Ducharme and colleagues [28], use of lower maintenance dose of ICS, or it may simply suggest that enrolled children were not comparable to those previously enrolled in placebo-controlled trials.

The paucity of trials prevents firm conclusions regarding the superiority or equivalence of intermittent versus daily ICS in patients with mild asthma and particularly with characteristics of patients that should be treated with each strategy. The superiority of daily ICS on several markers of asthma control would support the international consensus guidelines to recommend daily ICS as preferred therapy in patients with mild persistent asthma. Long-term (>one year) high methodological quality parallel-group trials using newer molecules would help address the concern about lung function decline and impact on the risk of exacerbations. Until then, therapy with intermittent ICS should probably be considered as a therapeutic trial with careful patient follow-up.

This review summarizes the best evidence available up to October 2012 derived from a systematic search of all eligible trials and unpublished reports, which minimizes the risk of inclusion bias. The results are derived from 6 trials of high methodological quality and we obtained additional unpublished data from authors that strengthened the meta-analysis.

We acknowledge the following limitations. The data is heavily weighted towards preschoolers and children who together represented 68% of individuals. In addition, the review pooled adults, school-aged

children, and preschoolers which improves generalizability. While we identify little heterogeneity in results, we acknowledge that the small number of trials prevented our ability to subgroup differences in the response to either intervention associated with age or atopy or other patient characteristics. While the whole age spectrum covered, with only two trials in each age group we cannot assume representativeness of studied patients. We also acknowledge the possibility of misclassification due to within-patient and between-physician variability in phenotyping of preschoolers, because of the difficulty in firmly distinguishing mild persistent versus intermittent asthma, without lung function tests in this young age group [29]; this uncertainty may have led to the inclusion of an unknown proportion of preschool-aged children with intermittent viral-induced asthma that may have diluted the effect. Yet, the exclusion of preschoolers did not change the conclusions. Several additional differences across trials regarding age, other patient characteristics, different ICS molecules, and step-up protocols during exacerbations raise the question about the wisdom of aggregating all trials; however, the lack of heterogeneity of pooled trials across nearly all outcomes argued for aggregation of data.

The results are applicable to school-aged children and adults with symptomatic mild persistent asthma and preschoolers with suspected persistent asthma due to the repeated wheezing, with or without interim symptoms (or positive asthma predictive index). Two ICS molecules used, beclomethasone dipropionate or budesonide, are known for their growth suppressing effects in children [26,30]; it is unclear whether similar or lesser effect on growth would have been observed with fluticasone propionate or newer molecules such as ciclesonide and mometasone at equivalent doses. Consequently, caution is advised not to blindly attribute the observed growth suppression to the maintenance ICS strategy *per se*, without recognizing that the results may be limited to beclomethasone dipropionate and budesonide. Importantly, as trials lasted one year at most, the long-term impact of intermittent ICS on lung growth in children, lung function decline, and irreversible airway remodeling over the following five to 10 years remain important, yet unaddressed, concerns in children and adults [31,32].

In conclusion, a firm recommendation can not be made to support the superiority or the equivalence of maintenance versus intermittent ICS to prevent or reduce the severity of exacerbations in patients with mild persistent asthma. Markers of asthma control, lung function and airway inflammation supported the superiority of maintenance over intermittent ICS. The small, but statistically significant, growth suppression observed with maintenance beclomethasone dipropionate and budesonide underlines the need to select the safest and lowest effective dose of ICS, particularly in children. Until further data are available, we recommend to carefully weigh the potential benefits and harms and to monitor the individual patients' asthma control, lung function, and exacerbations, in order to regularly re-assess the appropriateness of selected therapy.

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Conflict of Interest

Bhupendrasinh Chauhan received a post doctoral scholarship from one of Prof. Ducharme's grants from the Canadian Institute of Health Research and has no conflict. Dr. Caroline Chartrand has no conflict. Prof. Francine Ducharme has received travel support, research funds and fees for speaking from AstraZeneca, Glaxo SmithKline, Novartis, Takeda, and Merck Frosst Inc.

References

1. Bozek A, Jarzab J (2011) Improved activity and mental function related to proper antiasthmatic treatment in elderly patients with Alzheimer's disease. Allergy Asthma Proc 32: 341-345.
2. Williams SG, Schmidt DK, Redd SC, Storms W, National Asthma Education and Prevention Program (2003) Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program. MMWR Recomm Rep 52: 1-8.
3. Lougheed MD, Lemiere C, Ducharme FM, Licskai C, Dell SD, et al. (2012) Canadian Thoracic Society 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults. Can Respir J 19: 127-164.
4. British Thoracic Society, Scottish Intercollegiate Guidelines Network (2011) British guidelines on the management of asthma - A national clinical guideline. British Thoracic Society.
5. Menckeberg TT, Bouvy ML, Bracke M, Hugtenburg JG, Lammers JW, et al. (2008) Patients' understanding of the reasons for starting and discontinuing inhaled corticosteroids. Br J Clin Pharmacol 66: 255-260.
6. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, et al. (2004) Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol 114: 1288-1293.
7. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, et al. (1996) Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 98: 1051-1057.
8. Pando S, Lemiere C, Beauchesne MF, Perreault S, Forget A, et al. (2010) Suboptimal use of inhaled corticosteroids in children with persistent asthma: inadequate prescription, poor drug adherence, or both? Pharmacotherapy 30: 1109-1116.
9. Blais L, Kettani FZ, Beauchesne MF, Lemière C, Perreault S, et al. (2011) New measure of adherence adjusted for prescription patterns: the case of adults with asthma treated with inhaled corticosteroid monotherapy. Ann Pharmacother 45: 335-341.
10. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, et al. (2005) Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med 352: 1519-1528.
11. Papi A, Nicolini G, Baraldi E, Boner AL, Cutrera R, et al. (2009) Regular vs prn nebulized treatment in wheeze preschool children. Allergy 64: 1463-1471.
12. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, et al. (2011) Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med 365: 1990-2001.
13. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, et al. (2011) Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet 377: 650-657.
14. Turpeinen M, Nikander K, Pelkonen AS, Syvänen P, Sorva R, et al. (2008) Daily versus as-needed inhaled corticosteroid for mild persistent asthma (The Helsinki early intervention childhood asthma study). Arch Dis Child 93: 654-659.
15. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, et al. (2007) Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 356: 2040-2052.
16. Chauhan BF, Chartrand C, Ducharme FM (2012) Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. Cochrane Database System Rev: 12.
17. Chauhan BF, Chartrand C, Ducharme FM (2013) Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. Cochrane Database System Rev: 2.
18. Higgins JPT, Green S (2009) Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. The Cochrane Collaboration.
19. Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gern J, et al. (2012) International consensus on (ICON) pediatric asthma. Allergy 67: 976-997.
20. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21: 1539-1558.
21. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177-188.

22. Review Manager (RevMan) Version 5.1 (2008) [Computer program].

23. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD (2000) A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 162: 1403-1406.

24. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleecker ER, et al. (2012) Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. JAMA 308: 987-997.

25. Quon BS, Fitzgerald JM, Lemiere C, Shahidi N, Ducharme FM (2010) Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Cochrane Database Syst Rev 10: CD007524.

26. Sharek PJ, Bergman DA (2000) The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Pediatrics 106: E8.

27. The Childhood Asthma Management Program Research Group (2000) Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med 343: 1054-1063.

28. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, et al. (2009) Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med 360: 339-353.

29. Ducharme FM, Morin J, Davis GM, Gingras J, Noya FJ (2012) High physician adherence to phenotype-specific asthma guidelines, but large variability in phenotype assessment in children. Curr Med Res Opin 28: 1561-1570.

30. Priftis KN, Papadimitriou A, Gatsopoulou E, Yiallouros PK, Fretzayas A, et al. (2006) The effect of inhaled budesonide on adrenal and growth suppression in asthmatic children. Eur Respir J 27: 316-320.

31. Sears MR (2007) Lung function decline in asthma. Eur Respir J 30: 411-413.

32. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW, et al. (2009) Severe exacerbations and decline in lung function in asthma. Am J Respir Crit Care Med 179: 19-24.

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