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 asymptomatic and restart treatment when deemed required, that is, at the patients often discontinue their maintenance ICS treatment when

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 β2-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 (χ²) test for heterogeneity and the I² statistic; P<0.10 or an I²>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 (Table 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 β2-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 β2-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...
to intermittent or maintenance ICS; in such 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; χ² 1.61, df 2, P 0.45), baseline severity (mild versus moderate airway obstruction; χ² 0.81; df 1; P 0.37), ICS dose during exacerbation (χ² 0.63, df 3, P 0.89), or trial duration (12-24 versus 44-52 weeks; χ² 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 β₂-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; χ² 0.90, df 2, P 0.66), baseline severity (χ² 0.84; df 1; P 0.36), or ICS step-up protocol during exacerbation (χ² 1.08, df 3, P 0.78). Due to homogeneity of trials...
Asthma, the risk of experiencing an exacerbation requiring rescue inhaled beclomethasone dipropionate or budesonide. These benefits were observed at the cost of small, but significant, growth suppression in children receiving maintenance, instead of intermittent, ICS. All statistically significant, the magnitude of benefit of maintenance over intermittent ICS was clinically more important on asthma control days (7% greater increase in asthma control days and 9% greater increase in symptom-free days) than on lung function and rescue β2-agonist use.

**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 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).

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.

![Risk Ratio Graph](image)

**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.

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
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 β₂-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 as noted previously by Ducharme and colleagues [28], 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

Table 2: Secondary outcomes.

| 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                                                                   | 383   | 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; FEV₁: Forced Expiratory Volume In One Second; NO: Nitric Oxide.
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 cannot 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 Frost Inc.

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