Daily inhaled corticosteroids or montelukast for preschoolers with asthma or recurrent wheezing: A systematic review

Jose A. Castro-Rodriguez MD, PhD | Carlos E. Rodriguez-Martinez MD, MSc | Francine M. Ducharme MD

Abstract

Background: Most international asthma guidelines recommend that children ≤5 years with asthma or recurrent wheezing be treated with daily low- moderate dose inhaled corticosteroids (ICS) as the preferred controller and leukotriene receptor antagonists (LTRA) as alternative therapy. There is no systematic review comparing the efficacy of ICS versus LTRA monotherapy in this age group.

Objective: To compare the efficacy of daily ICS versus LTRA in preschoolers with asthma or recurrent wheezing.

Methods: Randomized, prospective, controlled trials published by December 2017, with a minimum of 3-month therapy with daily ICS versus LTRA were identified. The co-primary outcomes were the number of wheezing episodes and daily symptom score. Secondary outcomes included unscheduled emergency visits, need of rescue systemic corticosteroids (SC), hospitalization for exacerbations, lung function, and adverse effects.

Results: Of 29 trials identified, six studies (n = 3204 patients, 62% males, age range: 6-54 months) met the inclusion criteria; two were at low risk of bias. Five pertained to children with asthma; one to those with recurrent wheezing. No outcomes were similarly reported in the six studies, preventing meta-analysis. Based on trials at lowest risk of bias and the largest open-labelled studies, ICS was associated with better control of symptoms and less exacerbations than LTRA. And also less need for rescue SC. Insufficient data of high quality prevented firm conclusions on other secondary outcomes.

Conclusions: In preschoolers with asthma or recurrent wheezing, daily ICS appears more effective than daily LTRA for improving symptom control and decreasing exacerbations, particularly those requiring rescue SC, although the magnitude of benefit remains to be quantified.

Keywords

inhaled corticosteroids, meta-analysis, montelukast, persistent asthma, preschoolers, systematic review

Abbreviations: API, asthma predictive index; CI, confidence interval; ED, emergency department; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; NAEPP, National Asthma Education and Prevention Program; pMDI, pressurized metered-dose inhalers; RCT, randomized controlled trial; RR, relative risk; SC, systemic corticosteroids; WMD, weighted mean difference.
INTRODUCTION

Most national and international asthma guidelines, for example, NAEPP, NAEPP, BTS/SIGN, GINA, and Canadian recommend that children ≤5 years of age with persistent or recurrent asthma-like symptoms (step 2) be treated with an asthma controller using daily low-moderate dose of inhaled corticosteroids (ICS) as the preferred controller, and leukotriene receptor antagonists (LTRA) as alternative.

Effective management options for early-life asthma/wheeze is of great importance for a number of reasons. First, the burden of disease is greatest in preschoolers with a higher proportion of emergency department (ED) visits as well as more hospitalizations, sleep disturbances, and limitation of play and family activities, than older children. Second, irreversible impairment in lung function demonstrated by the age of 6 years in children with preschool wheeze suggests a window of opportunity to perhaps prevent irreversible damage. Indeed, it is possible that the repeated and cumulative lung injury caused by repeated wheezing, particularly when associated with respiratory infections and atopy, maybe causal or at least, be an important factor affecting lung growth and asthma persistence.

Although most international guidelines suggest ICS as the preferred drug over LTRA for preschoolers with asthma or recurrent wheezing, there are no published systematic reviews comparing the efficacy of ICS versus LTRA limited to children aged 5 years and younger to firmly support this recommendation. Therefore, the objective of this systematic review was to compare the efficacy of ICS versus LTRA monotherapy in preschoolers with asthma or recurrent wheezing.

METHODS

Search and selection criteria

We searched electronic databases (up to December 2017) namely, MEDLINE, CENTRAL (Cochrane Collaboration clinical trials register), EMBASE, and Latin-America LILACS. The search process was conducted in conjunction with library electronic search specialists using the keywords: "(montelukast or antileukotrienes) and (ICS or budesonide or fluticasone or betamethasone or ciclesonide or flunisolide) and (asthma or wheeze)," filtered by “Randomized Controlled Trial (RCT), Clinical Trial, Humans," and “Preschool Child: 2-5 years or Infant: birth-23 months." In addition, we searched other non-bibliographic data sources, references of identified publications, and pharmaceutical industry web sites. The inclusion criteria for trials were: parallel group or crossover RCTs without any restriction on language of publication, involving children aged 5 years or less, with asthma or recurrent wheezing; and comparing any daily ICS (any molecule) with daily LTRA monotherapy, for a minimum of 3 months. Trials were excluded if they: (1) included school children or adolescents; (2) had used ICS or LTRA in the 3 months prior to enrollment; and (3) were published only in the form of letters or abstracts. The co-primary outcomes of the study were the number of wheezing/asthma episodes and daily symptom score. Secondary outcomes included unscheduled visits to the ED, rescue systemic corticosteroids (SC), hospitalization for exacerbations, improvement of lung function, and adverse effects (AEs). The trial has been registered with the international prospective register of systematic reviews (PROSPERO, #CRD42017082077).

Data abstraction and assessment of risk of bias

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA). Titles, abstracts, and citations were independently analyzed by two independent investigators (JAC-R, CR-M). From the full texts, the reviewers independently assessed all studies for inclusion based on the including and exclusion criteria for study design, population, intervention, and outcomes. Disagreements were resolved through a mediator (FMD). Two authors independently assessed the risk of bias of included studies based the Cochrane Handbook risk of bias tool, based on the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias, including industry funding.

Data analysis

The planned meta-analysis involved a random-effects meta-analysis using Review Manager 5.1.2 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, Copenhagen, Denmark) and ascertainment of heterogeneity using the I² test and chi square. Several a priori subgroup analyses were planned including: age (<2 years vs >2 years), allergic versus non-allergic patients, comparison between different types of ICS and route of administration, and pharmaceutical industry versus independent sponsor. Unfortunately, due to no or inconsistent reporting of outcomes, a meta-analysis or subgroup analyses could not be performed. Instead, a descriptive synthesis of individual trial results of our a-priori specified primary and secondary outcomes was performed. A P < 0.05 using a 2-tailed test or 95% confidence interval excluding one for relative risk (dichotomous outcome) or 0 for weighted mean difference (continuous outcome) were deemed indicative of statistical significance.

RESULTS

Twenty-three of 29 potentially eligible studies were excluded because they failed to meet inclusion criteria or they had exclusion criteria, leaving six eligible trials. (Figure 1). These six trials were published between 2008 and 2016 (Table 1); two studies were conducted in US, and one each in Netherland, Poland, China, and Pakistan. A total of 3204 patients were randomized; 62% of patients were male and the age range from 6 to 54 months. Within each trial, the distribution for gender and age was similar between the ICS and LTRA groups. Five studies were conducted in
preschoolers aged at least 6 months with a diagnosis of asthma and the study by Krawiec et al\textsuperscript{13} enrolled children aged 6-36 months after their first to third wheezing episode (without specification of the distribution of the number of wheezing episodes among participants), hereafter referred to as recurrent wheezing. In all studies including asthmatic children, the authors justified the necessity of step two controller therapy based on different guidelines (two studies\textsuperscript{12,16} used NAEPP, one\textsuperscript{15} used GINA, one\textsuperscript{14} used PRACTALL) or "sufficient severity to justify the use of prophylactic asthma treatment"\textsuperscript{11} or prophylactic treatment was initiated after a hospitalization due to a severe wheezing episode in the remaining study.\textsuperscript{13}

Three trials\textsuperscript{11,12,16} used fluticasone propionate (FP) by pressurized metered-dose inhaler [pMDI] (50-100 µg/day), two studies\textsuperscript{12,14} administered budesonide by inhalation suspension (BIS) via a nebulizer (0.5 mg/day), and one\textsuperscript{15} did not specified the ICS used. All trials\textsuperscript{11-16} used montelukast (4-5 mg/day as per age-specific dosage) as the LTRA. In two studies,\textsuperscript{11,13} children were treated for 3 months, in two trials,\textsuperscript{14,15} for 6 months, and in the remaining two trials,\textsuperscript{12,16} for almost 12 months. One trial\textsuperscript{11} had an additional placebo group, and one\textsuperscript{13} an additional untreated group. Only one trial\textsuperscript{16} documented self-reported adherence, which was 96% or greater for ICS and montelukast. Additional details on specific treatment interventions, doses, and duration are listed in Table 1.

Two trials\textsuperscript{11,12} were sponsored by the pharmaceutical industry, one\textsuperscript{16} by the National Heart, Lung, and Blood Institute, and the remaining three\textsuperscript{13,14,15} failed to specify the funder. All trials were reported as randomized studies, although no description of the allocation concealment was provided in four of them.\textsuperscript{12-15} In two studies,\textsuperscript{11,14} both the participants and study personnel were blind to the intervention.

Five studies\textsuperscript{11-15} had a parallel and one\textsuperscript{16} had a crossover design. In terms of risk of bias, only two studies, namely that of Kooi et al\textsuperscript{11} and Fitzpatrick and colleagues\textsuperscript{16} were considered to be at low risk of bias. The remaining four studies\textsuperscript{12-15} were at high risk of bias primarily due to the allocation concealment, blinding, and incomplete data reporting issues (Table 2).

**Primary outcomes**

Due to the inability to conduct a meta-analysis for any primary outcomes, we report a narrative synthesis of these outcomes. The number of asthma/wheezeing episodes was reported in two trials,\textsuperscript{12,13} but using different parameters. In a three-arm trial (n = 70), Krawiec et al\textsuperscript{13} reported no difference in the number and percentage of episodes among those who receive either montelukast (4 mg qd), FP (100 µg bid), or no treatment for 3 months of treatment. In contrast, the post-hoc analysis of the open-label trial by Szefler et al\textsuperscript{12} focusing on the 202 preschoolers, reporting a 41% lower rate (number/patient/year) of mild and severe exacerbations in the group receiving BIS (0.5 mg qd) compared to montelukast (4 mg qd group) (1.35 vs 2.30, \( P = 0.003 \)).

Daily symptom score was reported in four trials,\textsuperscript{11,12,14,16} but each using different scales. In a three-arm trial (n = 63), Kooi et al\textsuperscript{11} reported a significant greater improvement in daily symptom score with FP (100 µg bid) than placebo (\( P = 0.021 \)) after 3 months of treatment, but no significant differences between FP and montelukast (4 mg qd) or between montelukast and placebo. In Szefler et al\textsuperscript{12} trial, no group difference was observed in symptoms reported in an electronic diary at 12 week between BIS (0.5 mg qd) versus montelukast (4 mg qd). Li et al\textsuperscript{14} (n = 239) reported a significantly decrease in asthma symptom

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**FIGURE 1** Process of study selection

![Process of study selection diagram](image-url)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design/location</th>
<th>Diagnosis</th>
<th># patients (%male)</th>
<th>Age, ICS group</th>
<th>Age, MONT group</th>
<th>Comparisons</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Significant results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kooi et al,11</td>
<td>Netherland</td>
<td>Asthma</td>
<td>63 (62)</td>
<td>3.9 ± 1.1 yr</td>
<td>3.8 ± 1.4 yr</td>
<td>FP 100 µg BID; or MONT 4mg QD; or placebo; for 3 months</td>
<td>Daily symptoms score</td>
<td>Rescue medication; Blood eosinophils; Lung function &amp; FOT</td>
<td>Improved daily symptoms score in FP versus placebo (P = 0.02), decrease blood eosinophils in MONT versus placebo (P = 0.045), decrease FOTat 4-24 Hz resistance measured by forced in FP versus MONT (P = 0.048)</td>
</tr>
<tr>
<td>Szefler et al,12</td>
<td>US</td>
<td>Asthma</td>
<td>202 (65)</td>
<td>3 ± 0.87 yr</td>
<td>3 ± 0.85 yr</td>
<td>BIS 0.5 mg QD; or MONT 4mg QD; for 52 weeks</td>
<td>Time for first additional asthma medication for mild or severe exacerbation at 12 &amp; 26 wk; time for the first mild &amp; severe exacerbation at 12, 26, 52 wk; rate of mild &amp; severe exacerbation over 52 wk</td>
<td>Time for first additional asthma medication for mild or severe exacerbation at 12, 26, 52 wk; time for the first mild &amp; severe exacerbation at 12, 26, 52 wk; rate of mild &amp; severe exacerbation over 52 wk</td>
<td>Less % patients used additional asthma medication at 12 mo in BIS versus MONT (34.3 vs 48.5%, P = 0.05); Less % patients need OCS at 12, 26, and 52 wks in BIS versus MONT (8.6 vs 18.6%, P = 0.04; 14.3 vs 27.8%, P = 0.03; 21.9 versus 37.1%, P = 0.02); Less rate of additional courses of medication in BIS versus MONT (1.25 vs 2.30, P = 0.003, or an estimated reduction of 41%)</td>
</tr>
<tr>
<td>Krawiec et al,13</td>
<td>Poland</td>
<td>Recurrent wheezing</td>
<td>70 (64)</td>
<td>18 (9-24) mo</td>
<td>18 (9-25) mo</td>
<td>FP50-100 µg BID; or MONT 4mg QD; for 3 months</td>
<td>Wheezing episodes/1 yr; % children wheezing episodes/3 mo; #hospitalization/3mo/1 yr</td>
<td>No differences among FP, MK or non-treatment group for any outcomes</td>
<td></td>
</tr>
<tr>
<td>Li et al,14</td>
<td>China</td>
<td>Asthma</td>
<td>239 (62)</td>
<td>31 ± 14 mo +API, 32 ± 13 mo-API</td>
<td>38 ± 16 mo +API, 37 ± 13 mo-API</td>
<td>BIS 0.5 mg BID for 4 wk and 0.5 mg OD up to 24 wk; or MONT 4mg QD; for 24 weeks</td>
<td>Daytime &amp; nighttime asthma symptoms score up to 24 wk</td>
<td>Among +API children: Improve daily asthma symptoms score in MONT versus BIS at 12 wk (P = 0.03) and at 24 wk (P = 0.046). Among -API children: no differences</td>
<td></td>
</tr>
<tr>
<td>Jehan et al,15</td>
<td>Pakistan</td>
<td>Asthma</td>
<td>2400 (58)</td>
<td>2.4 ± 1.2 yr</td>
<td></td>
<td>ICS 200 µg/d; or MONT 4-5 mg QD; for 6 months</td>
<td>Control asthma (by GINA)</td>
<td></td>
<td>More patients step-up of treatment in MONT versus ICS (32.1 vs 6.4%); less patients step-down in MONT versus ICS (6.8 vs 51.6%).</td>
</tr>
<tr>
<td>Fitzpatrick et al,16</td>
<td>US</td>
<td>Asthma</td>
<td>230 (62)</td>
<td>39.7 ± 13 mo</td>
<td></td>
<td>Daily FP 44 µg/BID for 16 wk; or as-needed FP 44 µg/ BID + albuterol</td>
<td>Differential response in time for first asthma exacerbation</td>
<td>Exacerbations, asthma control days, albuterol use, unscheduled health care for asthma, treatment failures.</td>
<td>Probability of best response was highest on daily FP than as-needed FP or MONT (P &lt; 0.0001). Daily FP was associated with more asthma control days, less</td>
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(Continues)
score with montelukast (4 mg, qd) than with BIS (1 mg qd) at 12 and 24 weeks of treatment (0.8 ± 0.4 vs 1.5 ± 0.9, *P* = 0.032 and 0.7 ± 0.4 vs 1.1 ± 0.9, *P* = 0.046, respectively) in patients with a positive asthma predictive index (API), although no difference was found in preschoolers with a negative API and no overall analysis was done combining API positive and negative groups. Finally, Fitzpatrick et al. in a large cross-over trial (n = 230), using a composite measure of asthma control (time for first asthma exacerbation required SC and annualized number of asthma control days), reported a highest probability of best response (*P* < 0.0001) when the same child received daily FP (88 µg bid), compared to daily montelukast (4 mg qd) or as-needed FP (FP 88 µg bid plus albuterol 180 mg). In summary, based on the trials at the lowest risk of bias contributing data, children treated with ICS experienced greater symptom control than with placebo and had a higher probability of best response compared to montelukast or as needed ICS with.

### Secondary outcomes

The number of trials contributing data to our secondary outcomes was: two for rescue SC, two for hospitalization, two for the change in lung function, one study reported unscheduled visits to the ED, and four trials reported AEs. Due to the inability to conduct a meta-analysis for any secondary outcomes, we only report a descriptive synthesis of these outcomes.

With regards to rescue SC, Szefler and colleagues reported significantly fewer patients in the BIS (0.5 mg qd) group needing rescue SC at 12, 26, and 52 weeks of treatment than those on montelukast (8.6% vs 18.6%, *P* = 0.04; 14.3% vs 27.8%, *P* = 0.03; 21.9% vs 37.1%, *P* = 0.02). Similarly, Fitzpatrick et al. reported significantly fewer episodes requiring rescue SC when children were treated with daily FP (19% vs 34%, *P* = 0.001) or with as needed FP (19% vs 28%, *P* = 0.027).

No group difference in hospitalization rate between ICS versus montelukast were reported in the two trials. As for lung function, Kooi et al. reported a significant lower frequency dependence of resistance in the FP group compared to the montelukast group (*P* = 0.048) after 3 months of treatment; none of the remaining five oscillometry parameters showed any within- or between-group difference and there was no correction for multiple testing. In Szefler et al. study, the mean changes from baseline in the peak expiratory flow was similar between BIS versus montelukast after 12 months of treatment. There were no difference in the number of patients with a least one ED visit in one study.

As for reported AEs, the number of patients reporting an upper respiratory tract infection was significantly higher in the montelukast and FP groups than in the placebo group (*P* = 0.011) in Kooi’s study. In another study, AE reports were recorded in two children in the montelukast (skin rash) and two in the FP (thrush of the oral cavity) group. Finally, no difference in the number of children reporting cough was observed between daily FP (n = 3), as-needed FP (n = 4), and daily montelukast (n = 1) and no group difference in height velocity was reported in Fitzpatrick et al’s trial. In the only study,
reporting study discontinuation due to severe AEs, no discontinuations were observed in the ICS group whereas 4 discontinuations were reported with montelukast (asthma [n = 2], pneumonia [1], and URTI [1]).

Other outcomes described in the included studies but not a priori specified in the protocol

Jehan et al\textsuperscript{15} randomized 2400 Pakistani children with uncontrolled asthma to ICS or montelukast for 6 months. After 6 months of treatment, 51.6% of children on ICS versus 16.7% on montelukast (P < 0.001) stepped-down therapy, whereas 6.4% of children on ICS versus 32.1% on montelukast (P < 0.001) were stepped-up therapy. In the study by Szefer et al,\textsuperscript{12} the rate (number/patient/year) of additional asthma medication for mild or severe asthma exacerbation was significantly lower (by an estimated 41%) in the BIS versus montelukast group (1.35 vs 2.30, P = 0.003, respectively). In a sub-analysis of Fitzpatrick’s large cross-over RCT,\textsuperscript{16} the probability of best response (time for first asthma exacerbation required SC and annualized number of asthma control days) with daily FP compared to as-needed FP or daily montelukast occurred more if the children had both allergen sensitization and blood eosinophil counts of ≥300/\(\text{mL}\), but not in those with positive modified API;\textsuperscript{18} no specific phenotype for best response to daily montelukast was identified. The authors suggested that, for asthmatic preschoolers with type-2 inflammation (allergy) ICS should be the preferred therapy, but for those without type two inflammation, no specific therapy is identified.

**DISCUSSION**

Although it was not possible to perform a meta-analysis of pre-defined outcomes in the six RCTs (n = 3204) of preschoolers with asthma or recurrent wheezing comparing monotherapy of ICS versus LTRA, our systematic review revealed that ICS might be a better option than LTRA to control asthma daily symptoms. As one trial at low risk of bias favored ICS, whereas one at high risk of bias favored montelukast, and in the other two trials—one with low and the other with high risk of bias—both drugs show no group apparent difference. For the other co-primary outcome, number of wheezing/asthma episodes, ICS appears more effective to decrease exacerbations in RCTs with more than a low risk of bias, as one trial favored ICS and no differences were observed in the other. For the secondary outcome reduction of rescue SC, in two trials, including one at low risk of bias, favored to ICS than montelukast.

Three previous meta-analyses in preschoolers compared ICS versus placebo\textsuperscript{19} and montelukast versus placebo.\textsuperscript{20,21} One meta-analysis of 29 trials in preschoolers with recurrent wheezing or asthma confirmed that ICS was superior to placebo in preschoolers for reducing the incidence of wheezing/asthma exacerbations of any severity (18.0% vs 32.1%, \(P = 0.0001; I^2 = 10\%\)) with a number needed to treat (NNT) of 7 [95%CI: 6-9]); a post-hoc subgroup analysis suggested that this effect was higher in those with a diagnosis of asthma than wheeze, but it was not significantly affected by age (infants vs preschoolers), atopy, type of ICS, mode of delivery, study quality, and study duration. In addition, children treated with ICS had significantly fewer withdrawals caused by wheezing or asthma exacerbations, less albuterol use, and more clinical and functional improvement than those on placebo.\textsuperscript{19} Two meta-analyses found that montelukast was not superior to placebo in reducing the number of wheezing episodes among preschoolers with recurrent wheezing,\textsuperscript{20} nor in those with episodic viral wheeze.\textsuperscript{21}

In the present systematic review, one study\textsuperscript{11} at low risk of bias but with a small sample (n = 63) showed a significantly greater improvement in lung function (decrease FOT at 4-24 Hz resistance) with FP than with montelukast. The other study,\textsuperscript{16} with a low risk of bias and a large sample size (n = 230) demonstrated that ICS was more effective than montelukast in their primary outcome, a composite measure of asthma control (time for first asthma exacerbation required SC and annualized number of asthma control days). Similarly, the largest study,\textsuperscript{15} (n = 2400) reported significantly fewer preschoolers stepping-down the treatment when using ICS than montelukast, although less weight could be attributed to this study due to its open

<table>
<thead>
<tr>
<th>Source</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participant, personnel and outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
<th>Overall risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kool et al\textsuperscript{11}</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Krawiec et al\textsuperscript{13}</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
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<tr>
<td>Li et al\textsuperscript{14}</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
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<tr>
<td>Jehan et al\textsuperscript{15}</td>
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<td>High</td>
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<td>Fitzpatrick et al\textsuperscript{16}</td>
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</table>

The risk of bias in reported as high, low, or unclear for each criteria, as defined by the Cochrane Risk of Bias tool.\textsuperscript{9,32}
label design and incomplete reporting of outcomes. It is important to mention that the crossover trial by Fitzpatrick et al. suggested some patient heterogeneity in the magnitude of response to each drug and identified some characteristics of children who responded better to ICS than to montelukast (namely, those with apparent type-2 inflammation, ie, allergen sensitization and higher eosinophil counts); however, no superior treatment response was observed in those without a type-2 inflammation, and montelukast was not better than ICS in any patient subgroup. A previous study, on preschoolers with recurrent wheezing episodes reported that the ALOX5 5/5 genotype polymorphism identify a subgroup slightly more responsive to intermittent montelukast than placebo, suggesting a potential genetic determinant of response.

Interestingly, in the present review, no significant increased risk of AEs was detected using ICS versus montelukast in the four trials and no difference in height velocity was observed in preschoolers receiving daily FP (88 µg bid), as-needed ICS or daily montelukast.

When choosing a controller treatment for chronic disease such as asthma, it is important to consider the cost-effectiveness, in addition to efficacy, real-life effectiveness, and safety of each option. Different studies performed in adults as well as in pediatric patients, have demonstrated that, in patients with mild-to-moderate persistent asthma, ICS have a lower cost and higher effectiveness compared with LTRA (montelukast or zafirlukast). An exception to this statement might occur when adequate ICS adherence cannot be achieved, in which case an economic evaluation based on administrative claims data from US commercial health plans found that LTRA may be a reasonable choice as monotherapy. Whether this also applies to preschoolers remains to be determined.

We acknowledge the following limitations of the present review. Whereas five trials used the international guidelines to define asthma and the requirement for step 2 therapy, it is possible that some children had very mild symptoms, explaining the absence of a significant group difference in many trials. We included the remainder study that enrolled children age 6-36 months with their first up to the third episode of preschool wheeze admitted to the hospital; without the authors’ specification of, or subgroup analyses on, the number of wheezing episodes; we cannot exclude the possibility that some patients could have had bronchiolitis, which is known to not respond to ICS or montelukast. This latter study contributed data to exacerbations and AE, but due to its high risk of bias, did not influence our conclusion. Only one study at low risk of bias described patient-reported adherence; with high adherence to both daily medications, where ICS was superior to montelukast. In contrast, real-life unblinded pediatric studies usually report greater adherence to montelukast than ICS, often showing better or at least similar health outcomes with montelukast than ICS. The possibility of a differential adherence rate to study drugs in the remaining trials not documenting adherence, may potentially contribute to the apparent lack of group difference. Finally, the use of different metrics in the six included studies precluding a meta-analysis. Therefore, the conclusions were based on co-primary outcomes, without any quantification of effect, with more weight given to trials at lowest risk of bias (efficacy), acknowledging that large open-labelled studies are more likely to represent real-life effectiveness. The conclusions of the review should be interpreted in the light of the appalling paucity of trials and particularly of studies at low risk of bias in this age group despite more than 15 years of ICS and LTRA commercialization, combined with the use of different metrics and inconsistent reporting of outcomes that prevented meta-analysis to quantify benefit.

Therefore, additional studies at a low-risk of bias are clearly warranted to compare the efficacy of ICS versus montelukast in preschoolers with asthma or recurrent wheezing. Parallel-group trials with standardized reporting of outcomes would allow better quantification of the magnitude of effect for various efficacy and safety outcomes and more cross-over trials are needed to establish solid evidence-based criteria on which to personalize the initial choice of monotherapy. It is particularly crucial to establish the best controller therapy in this young age group as asthmatic preschoolers have the highest morbidity, experiencing more exacerbations requiring SC and hospital admissions than other all other pediatric age groups, with many exhibiting irreversible lung function impairment by 6 years of age. Ideally, future studies should have sustained therapy for several years with long-term follow-up until the age of 6 years or more. Indeed, in the PEAK study, a parallel-group RCT comparing daily FP versus placebo in 285 preschoolers aged 2-3 years, cessation of FP after 2 years of treatment resulted in a loss of asthma control and a decline lung function comparable that observed in the placebo group. Thus, while use of daily ICS was highly effective for controlling asthma and preventing exacerbations in this study, it did not cure asthma, suggesting that ongoing use is required for sustained benefits.

In conclusion, in preschoolers with asthma or recurrent wheezing that required controller therapy, the use of daily ICS (by pMDI or inhalation suspension by nebulizer) appears more effective than daily oral montelukast particularly for symptom control and for decreasing the number of exacerbations, including those requiring rescue oral corticosteroids, although the magnitude of benefit remains to be quantified.

ACKNOWLEDGMENT

No external funding was secured for this study. No sponsorship from institutions or the pharmaceutical industry was provided to conduct this study.

CONFLICT OF INTEREST

In the last 24 months, JAC-R has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of AstraZeneca, Novomed, and Teva; CER-M has received travel support and fees for speaking from Abbott-Lafrancol and Quideca; and FMD has received unrestricted research funds from Astra Zeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Canada, and Novartis, honorarium for consultancy work from Astra Zeneca, Boehringer Ingelheim, and Sanofi; and honorarium as speaker from Boehringer Ingelheim and Astra Zeneca (China).
REFERENCES


