A Systematic Review of Long-Acting β2-Agonists Versus Higher Doses of Inhaled Corticosteroids in Asthma

abstract

OBJECTIVE: To compare the efficacy of inhaled corticosteroids (ICS) plus long-acting β2 agonist (LABA) versus higher doses of ICS in children/adolescents with uncontrolled persistent asthma.

METHODS: Randomized, prospective, controlled trials published January 1996 to January 2012 with a minimum of 4 weeks of LABA +ICS versus higher doses of ICS were retrieved through Medline, Embase, Central, and manufacturer's databases. The primary outcome was asthma exacerbations requiring systemic corticosteroids; secondary outcomes were the pulmonary function test (PEF), withdrawals during the treatment period, days without symptoms, use of rescue medication, and adverse events.

RESULTS: Nine studies (n = 1641 patients) met criteria for inclusion (7 compared LABA+ICS versus double ICS doses and 2 LABA+ICS versus higher than double ICS doses). There was no statistically significant difference in the number of patients with asthma exacerbations requiring systemic corticosteroids between children receiving LABA +ICS and those receiving higher doses of ICS (odds ratio = 0.76; 95% confidence interval: 0.48–1.22, P = .25, I^2 = 16%). In the subgroup analysis, patients receiving LABA+ICS showed a decreased risk of asthma exacerbations compared with higher than twice ICS doses (odds ratio = 0.48; 95% confidence interval: 0.28–0.82, P = .007, I^2= 0). Children treated with LABA+ICS had significantly higher PEF, less use of rescue medication, and higher short-term growth than those on higher ICS doses. There were no other significant differences in adverse events.

CONCLUSIONS: There were no statistically significant group differences between ICS+LABA and double doses of ICS in reducing the incidence of asthma exacerbations but it did decrease the risk comparing to higher than double doses of ICS. *Pediatrics* 2012;130:e650–e657

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KEY WORDS

asthma, children, adolescents, LABA, inhaled corticosteroids, efficacy

ABBREVIATIONS

AEs—adverse events
BDP—beclomethasone dipropionate
CI—confidence interval
FDA—Food and Drug Administration
FEV_1—flow expiratory volume in the first second
ICS—inhaled corticosteroids
LABA—long-acting β2 agonist
OR—odds ratio
PEF—peak expiratory flow
RCT—randomized controlled trial
RR—relative risk
WMD—weighted mean differences

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According to the most commonly used international asthma guidelines,[1–3] children with persistent asthma should be started on controller therapy with inhaled corticosteroids (ICS) as the preferred drug, with leukotriene modifiers (eg, montelukast) as an alternative for patients who are unable or unwilling to use ICS. A recent meta-analysis concludes that children receiving ICS showed a significantly decreased risk of asthma exacerbation requiring systemic corticosteroids than children receiving montelukast.[4] As well, children treated with ICS had significantly higher pulmonary function and better clinical parameters compared with those receiving montelukast.[4] Moreover, the latest study comparing ICS and montelukast showed that fluticasone (100 μg twice daily) was the most effective therapy; however, uncontrolled asthma occurred in more than 50% of the children, and 39% of the children had at least 1 asthma exacerbation that was treated with oral corticosteroids during a 48-week period.[5]

In cases where ICS is not sufficient to control the disease in children, international guidelines recommend increasing the dose of ICS or adding leukotriene modifiers or long-acting β agonists (LABAs).[1–3] A previous systematic review[6] showed that in children, but not in adults, LABA added to ICS had not significantly reduced the risk of exacerbations requiring a short course of systemic corticosteroids (relative risk [RR] = 1.28, 95% confidence interval [CI] 0.58–2.66) compared with the use of higher doses of ICS. Moreover, children could be almost 3 times more likely than adults to require oral steroids when they were treated with a LABA than with ICS; however, some children included in the meta-analysis came from trials performed in mixed population (children and adults together).

In recent years, more studies enrolling children exclusively have appeared in the literature. Therefore, it is important to know which option (increased doses of ICS or the addition of LABA) is better for step 3 of the guidelines for children when low doses of ICS do not control their asthma.

The objective of this systematic review was to assess the safety and efficacy of the LABA/ICS combination compared with an increased dose of ICS (double or greater) in children and adolescents with uncontrolled persistent asthma.

METHODS

Search and Selection Criteria

We identified studies from Medline, Embase (search January 2012), and the Cochrane Controlled Trials Register (CENTRAL) (search January 2012 databases using the following medical subject headings, full text, and keywords: long-acting β-2 agonists OR salmeterol OR formoterol OR indacaterol AND corticosteroids OR fluticasone OR budesonide OR ciclesonide OR mometasone OR beclomethasone OR flunisolide OR triamcinolone). The search was then limited with the terms children OR child OR pediatric OR adolescents OR infants OR preschoolers. As well, we performed a search of relevant unpublished files from drug manufacturer databases (http://gsk-clinicalstudyregister.com/result_compounds.jsp; http://www.astrazenecaclinicaltrials.com; and http://www.novartisclinicaltrials.com). Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed. The specific inclusion criteria were as follows: (1) children and adolescents aged 4 to 18 years with persistent asthma and having received ICS daily; (2) the addition of LABA to ICS compared with a higher doses of ICS; (3) studies with at least 4 weeks' duration; (4) randomized (parallel group or crossover) controlled trials (RCTs) without language restriction. The primary outcome of the study was proportion of subjects with asthma exacerbations requiring the use of systemic corticosteroids. Secondary outcome measures were the following: withdrawals during treatment period, pulmonary function tests (FEV_1 or PEF), days without asthma symptoms, use of rescue medication, adverse events (AEs), and severe AEs. A serious AE was defined as any untoward medical occurrence that sometimes results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability/incapacity.[7]

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.[8] Titles, abstracts, and citations were independently analyzed by all reviewers. From the full texts, the reviewers independently assessed all studies for inclusion based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. The authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. The latter was assessed according to recommendations outlined in the Cochrane Handbook.[9] Disagreements were resolved by group consensus. In the case of multiple published or unpublished reports, data from the most recent version were extracted.

Data Analysis

The present analysis was done by intention to treat with all participants, including withdrawals, to minimize bias owing to differences among groups. We calculated the Mantel-Haenszel odds ratios (ORs) and 95% CIs for binary outcomes. When effect estimates were significantly different between groups,

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the number needed to treat to benefit or to harm was obtained. Continuous outcomes were pooled using weighted mean differences (WMDs) and 95% CIs. Heterogeneity was measured by the I^2 test (<40% could be unimportant, 40% to 60% could be moderate, and 60% to 100% could be substantial).[10] Because selected studies differed in the mixes of participants and interventions, a random-effects meta-analysis was performed to address this variation across studies in all outcomes.[11] We used a priori subgroup analysis to explore the influence of the ICS dose (double versus more than double), type of LABA (salmeterol versus formoterol), length of treatment (<24 weeks versus ≥24 weeks), age range (4–11 vs 11–17 years), and severity of airway obstruction (prebronchodilator FEV_1; and morning and evening PEF from baseline) Subgroups were compared by using the interaction test.[12] Additional predefined sensitivity analyses were done to explore the influence on effect size of risk of bias (low-risk trials versus high-risk trials), and the statistical model (fixed versus random effects). A low-risk bias was defined as a minimum of 5 of 6 domains filled in an acceptable way. Publication bias of primary outcomes was evaluated by funnel plots.[13] A $P < .05$ using a 2-tailed test was considered to indicate significance. Meta-analysis was performed with Review Manager 5.1.2 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, Copenhagen, Denmark).

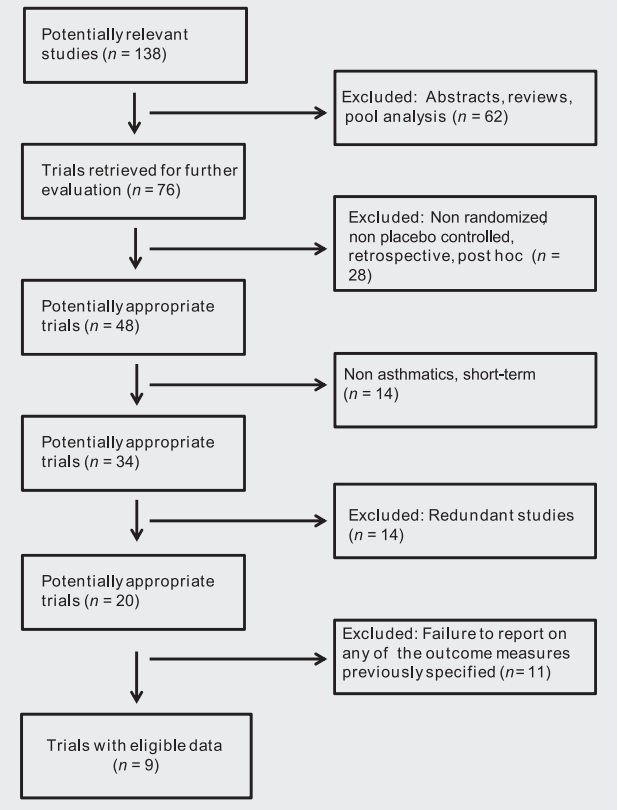

FIGURE 1
Process of study selection.

RESULTS

Nine RCTs,[14–22] involving a total of 1641 children and adolescents, fulfilled the inclusion criteria (Fig 1). One trial was unpublished.[20] All studies examined the combination LABA/ICS in 1 device (Table 1). The mean age of participants was 9 years (range 4–17), with 59% being male. Eight trials[14,16–22] included subjects with inadequately controlled asthma, low doses of ICS (200–500 μg/d beclomethasone dipropionate [BDP] or equivalent). The remaining study recruited children with mild asthma.[15] Almost all studies tested the commonly recommended doses of LABAs (ie, salmeterol 50 μg twice daily, or formoterol 9–12 μg twice daily). One study used the combination formoterol/budesonide as maintenance, plus additional doses as needed.[21] Intervention groups received BDP equivalent doses of 400 μg/d in 7 studies[14,16–20,22] and 200 μg/d in 2 studies.[15,21] The dose of ICS that the control group received was twice,[14–20] or more than twice, the amount received by the LABA/ICS group.[21,22] Rescue medications, such as inhaled short-acting β2-agonists and systemic steroids, were permitted in all the trials. Most of the studies[14,16–21] were funded by the pharmaceutical industry. Six studies[16–18,20–22] were judged to have a low risk of bias (successfully complied with at least 5 of the 6 domains of bias assessment) (Table 2).

Primary Outcome

The analysis of 8 studies (n = 1616 subjects)[14,16–22] showed no statistically significant differences in the number of patients with asthma exacerbations requiring systemic corticosteroids between children receiving LABA+ICS and those receiving higher doses of ICS (OR = 0.76; 95% CI: 0.48–1.22, P = .25) (Fig 2). There was no evidence of publication bias (Egger's test, 0.35; 95% CI: −0.4 to 0.74) or significant heterogeneity among studies (I^2 = 16%). However, among the subgroup studies that compared LABA+ICS versus higher than a double dose of ICS, combination therapy significantly reduced the risk of exacerbations (OR = 0.48; 95% CI: 0.28–0.82, P = .007, I^2 = 0%) (Fig 3B). This difference was compatible with a number needed

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TABLE 1 Characteristics of Included Studies

Study	Design	Location and Duration	Patients, *n*(% Male)	MeanAge, y (Range)	Atopy status (%)	Mean Baseline FEV_1 (% Predicted)	Selected Comparisons
Verberne[14]	R,DB,PG	Multicenter 54 wk	120 (63)	11.1 (6–16)	89	88.5	SALM/BDP 50/200 μg BID versus BDP 400 μg BID
Heuck[15]	R,DB,CO	SC 6 wk	27 (52)	9.6 (6–13)	NR	88.5	FORM/BUD 12/100 μg BID versus BUD 200 μg BID
Vaessen-Verberne[16] (SAM 101667)	R,DB,PG	Multicenter 26 wk	158 (58)	9.3 (6–16)	75	100	SALM/FLUT 50/100 μg BID versus FLUT 200 μg BID
de Blic[17] (SAM 104926)	R,DB,PG	Multicenter 12 wk	303 (64)	8.1 (4–11)	88	1.7 liters	SALM/FLUT 50/100 μg BID versus FLUT 200 μg BID
Gappa[18] (VIAPAED 102318)	R,DB,PG	Multicenter 8 wk	283 (68)	9.5 (4–16)	NR	91	SALM/FLUT 50/100 μg BID versus FLUT 200 μg BID
Murray[19] (SAM 40100)	R,DB,PG	Multicenter 6 wk	24 (50)	7.3 (4–11)	75	82	SALM/FLUT 50/100 μg BID versus FLUT 200 μg BID
GSK SAM 40012[20]	R,DB,PG	Multicenter 24 wk	367 (69)	7.7 (4–11)	75	NR	SALM/FLUT 50/100 μg BID versus FLUT 200 μg BID
Bisgaard[21] (SD-039-0673)	R,DB,PG	Multicenter 54 wk	224 (69)	8 (4–11)	NR	76	FORM/BUD 4.5/80 μg BID plus additional doses as needed versus BUD 320 μg BID
Lemanske[22]	R,DB,CO	Multicenter 16 wk	120 (40)	10.9 (6–17)	NR	96	SALM/FLUT 50/100 μg BID versus FLUT 250 μg BID

BID, twice daily; BUD, budesonide; CO, cross over; DB, double-blind; FEV_1= forced respiratory volume in the first second; FLUT, fluticasone; FORM, formoterol; NR, not reported; PG, parallel group; R, randomized; SALM, salmeterol; SC, single center.

TABLE 2 Risk of Bias of the Eligible Studies

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants & Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Reporting
Verberne 1998[14]	Y	Y	Y	Y	U	N
Heuck 2000[15]	Y	U	Y	Y	U	N
Vaessen-Verberne 2010[16]	Y	Y	Y	Y	U	Y
DeBlic 2009[17]	Y	Y	Y	Y	Y	Y
Gappa 2009[18]	Y	Y	Y	Y	Y	N
Murray 2010[19]	U	U	Y	Y	U	N
GSK SAM40012[20]	Y	Y	Y	Y	Y	N
Bisgaard 2006[21]	Y	Y	Y	Y	Y	N
Lemanske 2010[22]	Y	Y	Y	Y	Y	Y

N, No; U, Unknown; Y, Yes.

to treat of 9 (95% CI: 5–45). Post hoc subgroup analysis showed that subjects in studies testing higher than twice ICS doses had a significantly lower risk of asthma exacerbations than subjects in studies using a double ICS dose (OR = 0.38;95% CI: 0.37–0.84, $P = .01$).

A sensitivity analysis comparing age range groups (4–11 vs 11–17 years) was not possible to do, because the studies were not divided into these 2 age categories; in contrast, they had an age range not mutually exclusive (4–11 and 6–17 years). The duration of treatment (≥24 weeks versus <24 weeks) did not influence this effect size (OR = 0.53; 95% CI: 0.53–1.40, $P = .20$). Because the number of studies was low, the impact of the baseline severity of airway obstruction by lung function and type of LABA on size effect could not be examined. In the same way, the effect size obtained using random or fixed effects models did not differ (OR = 0.92; 95% CI: 0.42–2.19, $P = .9$). Sensitivity analysis based on the risk of bias showed different results; trials with low risk of bias[16–18,20–22] were not associated with a significantly low risk of exacerbation (OR = 0.68; 95% CI: 0.42–1.10, $I^2 = 8\%$) compared with trials with high risk of bias[14,15,19] (OR = 0.84; 95% CI: 0.12–5.75, $I^2 = 42\%$). There was no possibility of comparing trials sponsored by the pharmaceutical industry and independent studies, as only 1 of the 2 independent studies had data on exacerbations.

Secondary Outcomes

The addition of LABA to ICS provided significantly greater improvements in morning PEF from baseline (Fig 4A) (WMD = 8.74; 95% CI: 4.87–12.51 L/min, $I^2 = 0\%$) and evening PEF from baseline (WMD = 4.41; 95% CI: 1.77–7.05 L/min, $I^2 = 0\%$) at the end point (Fig 4B), compared with higher ICS doses. The duration of interventions did not affect the magnitude of this improvement over

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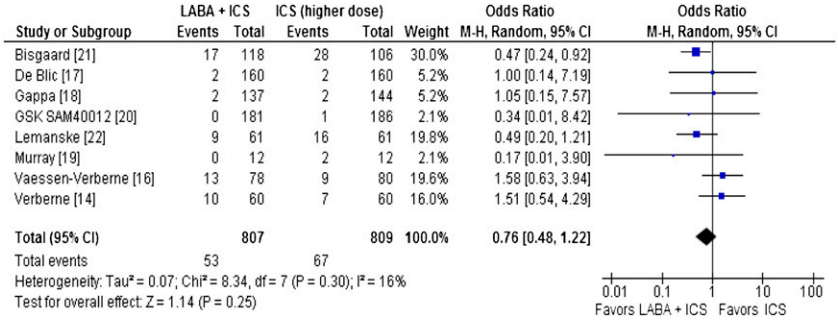

FIGURE 2

Pooled ORs and 95% CIs for the number of patients with at least 1 asthma exacerbation (with 95% CI) requiring systemic corticosteroids comparing LABA+ICS versus higher doses of ICS.

time. There were no statistically significant group differences in prebronchodilator FEV_1 between LABA+ICS versus higher ICS doses (WMD = 0.46; 95% CI: 0.18–1.34 L/s; I^2 = 74%, P = .68); however, this information came from only 3 studies.[14,16,17]

There were no significant differences between the LABA+ICS and ICS groups in the following outcomes: (1) number of prematurely discontinued patients (4.4% vs 4.1%); (2) withdrawals due to AEs (1.1% vs 1.1%); (3) withdrawals because of asthma exacerbations (0.3% vs 1.0%); (4) percentage of days free of asthma symptoms (WMD = –5.03% [–10.99 to 0.93]); (5) AEs (54.6% vs 55.6%); and (6) severe AEs (2.0% vs 2.6%) (Table 3). On the other hand, the combination of LABA+ICS is associated with significantly lower, but modest, use of rescue medication (–0.11 puffs/d, 95% CI: –0.20 to –0.01) (Table 3). Finally, data from 3 trials[15,16,21] showed that short-term growth was significantly greater in children treated with combination therapy compared with children treated with higher ICS doses (WMD = 0.66 cm/y [95% CI: 0.08–1.25) (Table 3). In almost all of the variables, the degree of heterogeneity was unimportant or null.

DISCUSSION

To our knowledge, this is the first meta-analysis performed of trials exclusively about child and adolescent populations to explore the efficacy of ICS+LABA compared with higher doses of ICS for uncontrolled persistent asthma. Overall, there were no statistically significant group differences between ICS+LABA and double or higher doses of ICS in reducing the incidence of asthma exacerbations requiring systemic corticosteroids.

Curiously, comparing 2 trials by using LABA+ICS versus higher than double doses of ICS, significant effects were observed that favor the combination therapy in reducing the risk of asthma exacerbation (number needed to treat of 9); however, the effect on asthma exacerbations was not observed when trials comparing LABA+ICS versus double doses of ICS were analyzed. The paradoxical effect is biologically difficult to explain. Potential explanation could be attributable to the inclusion of 2 particular studies. In the Bisgaard et al study,[21] 1 of the 2 groups with combination therapy used an adjustable

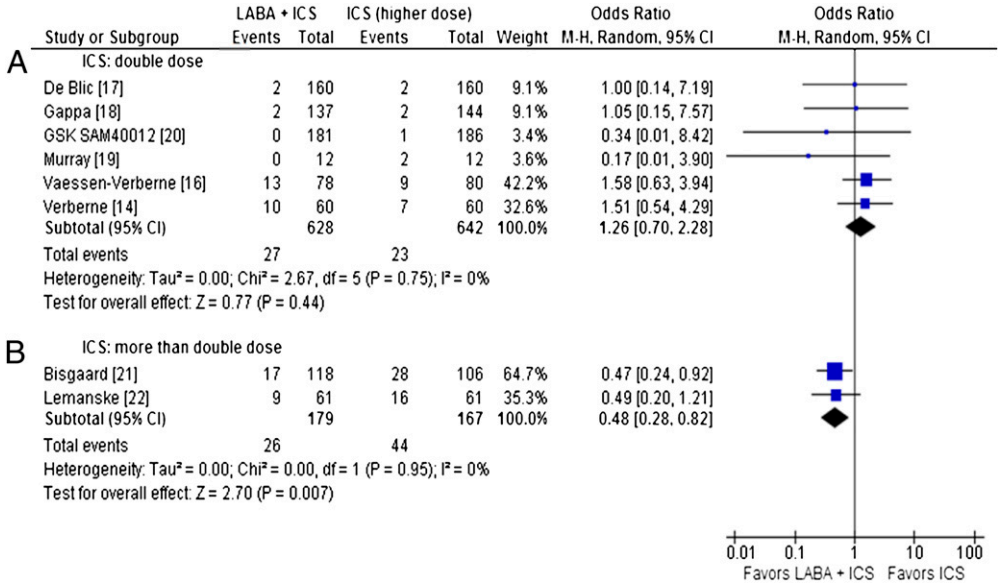

FIGURE 3

Pooled ORs and 95% CIs for the number of patients with at least 1 asthma exacerbation (with 95% CI) requiring systemic corticosteroids comparing LABA+ICS versus double (A) or more than double dose of ICS (B).

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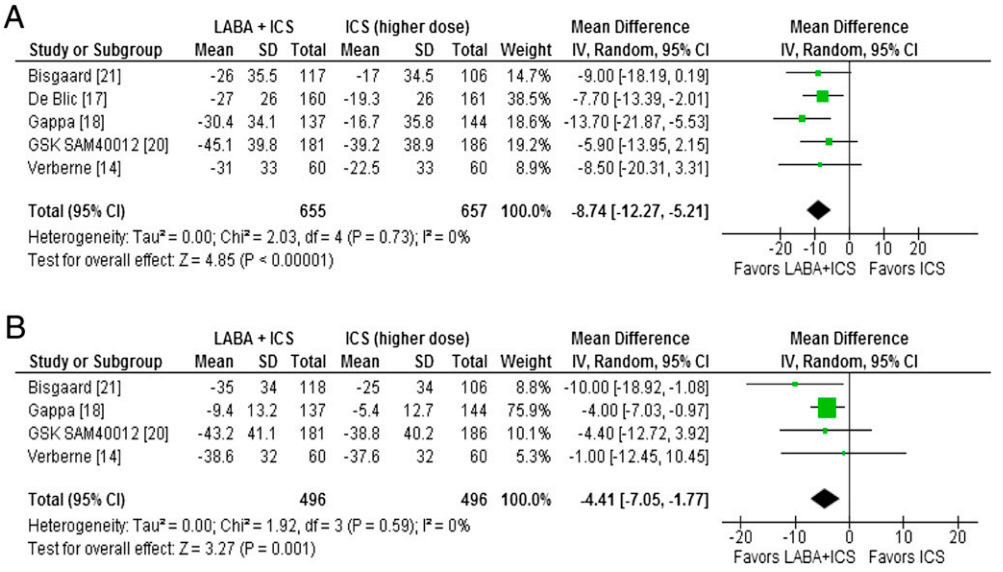

FIGURE 4
Pooled WMD and 95% CIs for the mean change in morning (A) and evening (B) PEF (L/min) from baseline.

TABLE 3 Effect of LABA plus ICS Versus Higher ICS Doses on Secondary Outcomes

Outcome	Studies	*n*	Measure (95% CI)	*P*	I^2
Prematurely discontinued patients	14–21	1543	OR = 1.0 (0.57 to 1.74)	.99	46
Withdrawals owing to adverse events	14–15, 17,21	713	OR = 1.01 (0.26 to 3.99)	.98	0
Withdrawals owing to asthma exacerbations	14,17,21	665	OR = 0.26 (0.04 to 1.63)	.15	0
Percent of days without asthma symptoms	14–16,18–21	1222	WMD = −5.03 (−10.99 to 0.93)	.10	0
Use of rescue medication, puffs/d	14–15,18–19,21	697	WMD = −0.11 (−0.20 to −0.01)	.02	0
AEs	14,16–21	1495	OR = 0.95 (0.73 to 1.25)	.23	25
Serious AEs	14,16–18,20–22	1593	OR = 0.76 (0.39 to 1.49)	.43	0
Linear growth rate, cm/y	15–16,21	430	WMD = 0.66 (0.08 to 1.25)	.02	0

n, number of subjects.

rather than fixed dose of LABA+ICS during exacerbations (and probably between exacerbations) or step-up therapy during exacerbation, versus those in the group of ICS who received fixed ICS doses, given the possibility that children in the latter group received a lower total ICS dose. And in the Lemanske et al study,[22] the design was cross sectional (child received for 16 weeks LABA+ 200 μg/d of fluticasone and for 16 weeks 500 μg/d of fluticasone or vice versa, with 4 weeks for wash-out) given the possibility that the wash-out period used was not enough. When we exclude these 2 studies in our meta-analysis, no statistically significant group difference on asthma exacerbation was found between LABA+ICS versus higher doses of ICS. It is important to consider that a crossover study is probably the best design to explore individual response to drugs, however, and that trial[22] showed the superiority of adding LABA to ICS versus higher doses of ICS in reducing asthma exacerbation requiring systemic corticosteroids.

Asthma exacerbations are common events in asthmatic patients and represent the greatest risk, and the highest asthma-related treatment cost for the health care system and for the community in general.[23] Also, exacerbations are the most important cause of lost school days for asthmatic children.[24] Asthma control has 2 aspects: current control in response to day-to-day symptoms through the use of rescue medications; and the burden imposed by these symptoms, and the risk of asthma exacerbations, irreversible decrease in lung function, and side effects from asthma medications.[2–25] Therefore, the prevention of asthma exacerbations is an important component of establishing ideal asthma control. A control trial[5] showed that in step 2 of asthma management (low ICS doses or leukotriene modifiers), more than 50% of children still have uncontrolled asthma and 39% have had at least 1 asthma exacerbation that was treated with oral corticosteroids during a 48-week period; for that reason it is very important to prevent exacerbations. A previous meta-analysis[6] that included only 3 studies done in children showed a trend toward increased risk of rescue oral steroids (RR 1.24, 95% CI: 0.58–2.66) and hospital admission (RR 2.21, 95% CI: 0.74–6.64) associated with combination

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therapy versus higher ICS doses. However, the current study included 8 trials done exclusively in children showing a trend of decreased risk of asthma exacerbations requiring systemic corticosteroids in the group of LABA+ICS versus higher doses of ICS (OR = 0.76; 95% CI: 0.48–1.22, P = .25). The difference may be attributable to the number and type of studies included. More trials need to be done to definitively lay down the best treatment in children with persistent asthma.

Another important direct effect of asthma exacerbations is the use of rescue medication and lung function deterioration.[26] In the current study, we found a significant modest reduction in the use of rescue medication among children on LABA+ICS than those on higher doses of ICS. Also, we found a statistically significant but uncertain clinically significant improvement in lung function (morning and evening PEF) among children/adolescents using LABA+ICS compared with those using higher doses of ICS. ICS treatment has a plateau, such that increasing the dose does not necessarily improve the clinical response, and systemic effects can start.[27] In contrast, the synergistic effect of adding LABA to ICS has been reported,[28,29] where LABA, along with its bronchodilator effect, increases the nuclear translocation of the glucocorticoid receptor. At the same time, ICS is delivered in the same device and along with its anti-inflammatory effect, it increases the expression of β2-receptors by increasing gene transcription. These findings could explain the higher performance of the combination of LABA+ICS versus higher doses of ICS.

We were not able to perform a subanalysis of main outcome comparing age groups (4–11 vs 11–17 years) because trials included in the meta-analysis had overlap in age (4–11 and 6–17 years). This is relevant because an international asthma guideline[1] recommends increasing ICS doses first instead of adding LABA in children older than 5 years. Moreover, if we found that short-term growth was significantly greater in children with combination therapy (370 μg/d of BDP or equivalent) compared with children with higher ICS doses (770 μg/d of BDP or equivalent), this difference of 0.66 cm/y could be important, especially for children in their early years. However, long-term growth studies need to confirm this finding. Also, it is important to consider the strong evidence of the ICS molecule-dependant effect on growth.[30]

Even though the studies included in the present meta-analysis have a wide range of duration (6 to 54 weeks), no statistically significant group differences in AEs and serious AEs were found between children on LABA+ICS versus higher doses of ICS. These findings are in accordance with the latest Food and Drug Administration (FDA) recommendation,[31,32] including 1 exclusively done in children by the FDA where those trials with LABA plus "assigned ICS therapy" showed no presence of LABA risk.[33] However, the FDA called on manufactures of LABA to conduct large clinical trials to definitively determine whether the addition of LABAs to ICS increases the risk of serious asthma outcomes.[34] Conversely, a recent study[32] has summarized nearly 20 systemic reviews and databases on LABA safety and showed that there is no risk of serious asthma-related events when using LABA associated with ICS, particularly when concomitant use of LABAs+ICS can be reasonably ensured (combined in a single inhaler). Evidence from RCTs, meta-analysis of RCTs, and observational studies, although limited by low statistical power, indicate that the use of combination therapy (LABAs+ICS) in children and adults is associated with a decreased risk of serious asthma-related events.[32]

CONCLUSIONS

This meta-analysis showed no statistically significant group differences between ICS+LABA and double doses of ICS in reducing the incidence of asthma exacerbations requiring systemic corticosteroids but it did decrease the risk comparing to higher than double doses of ICS. As well, children on combination therapy had significantly improved lung function (morning and evening PEF), reduced use of rescue medication and showed less effect on short-term linear grow rate than children on higher doses of ICS.

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