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Daily *vs.* intermittent inhaled corticosteroids for recurrent wheezing and mild persistent asthma: A systematic review with meta-analysis

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Summary
Background: Intermittent ICS treatment with SABA in response to symptoms, is an emerging strategy for control of mild-to-moderate asthma, and recurrent wheezing. This systematic revue compares the efficacy of daily vs. intermittent ICS among preschoolers, children and adults with persistent wheezing and mild to moderate stable persistent asthma.
Methods: Systematic review of randomized, placebo-controlled trials with a minimum of 8 weeks of daily (daily ICS with rescue SABA during exacerbations) vs. intermittent ICS (ICS plus SABA at the onset of symptoms), were retrieved through different databases. Primary outcome was asthma exacerbations; secondary outcomes were pulmonary function tests, symptoms, days without symptoms, SABA use, corticosteroids use, days without rescue medication use, expired nitric oxide and serious adverse events.
Results: Seven trials (1367 participants) met inclusion criteria there was no statistically significant difference in the rate of asthma exacerbations between those with daily vs. intermittent ICS (0.96; 95% CI: 0.86, 1.06, $I^2 = 0\%$). In the sub-group analysis, no differences were seen in duration of studies, step-up strategy or age. However, compared to intermittent ICS, the daily ICS group had a significant increase in asthma-free days and non-significant decreases in rescue SABA use and exhaled nitric oxide measurement.

Abbreviations: API, asthma predictive index; CI, confidence interval; FEV_1, forced volume in the first second; HR, hazard ratio; ICS, inhaled corticosteroids; MD, mean difference; PEF, peak expiratory flow; RR, risk ratio; SABA, short-acting beta2-agonists; SAE, serious adverse effects.

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Conclusions: No significant differences between daily and intermittent ICS in reducing the incidence of asthma exacerbations was found. However, the daily ICS strategy was superior in many secondary outcomes. Therefore, this study suggests to not change daily for intermittent ICS use among preschoolers, children with persistent wheezing and adults with mild-to-moderate stable persistent asthma. International prospective register of systematic reviews http://www.crd.york.ac.uk/PROSPERO/ (CRD42012003228).

Introduction

Current guidelines for chronic asthma management recommend the use of daily inhaled corticosteroids (ICS) as preferred treatment for preschoolers, children, adolescents and adults with recurrent wheezing and mild-to-moderate persistent asthma (mainly GINA 2 level).[1–3] In addition, they should use fast-acting rescue medications to relieve acute symptoms. This recommendation has been supported by studies reporting that such treatment improves physiological measures of airway obstruction, severity of symptoms, frequency of exacerbations and quality of life,[4,5] and has been reinforced by reports that continuous ICS treatment should prevent progressive loss of pulmonary function.[6,7]

However, intermittent or as-needed ICS treatment with short-acting beta2 agonists (SABA) in response to symptoms, is an emerging strategy for control of mild-to-moderate persistent asthma,[8] and recurrent wheezing.[9] Basing treatment on symptoms could reduce the amount of drug used, minimize the risk of adverse events, and reduce health care costs. Furthermore, ICS may rapidly exert their anti-inflammatory effects,[10] enhance the effect of beta2-agonists, and be as effective as systemic corticosteroids in treating asthma exacerbations. In particular, concerns about growth retardation, parental resistance, and patient adherence to a daily regimen of ICS promoted this new strategy.[11] Contrary, physicians prescribing intermittent ICS would give the wrong message to their patients about the chronicity of the disease. Thus, at present, we are seeing a significant controversy.[12,13]

Only one systematic review has been published on this topic.[14] The search of literature was conducted until December 2011, and authors included six studies with seven comparisons, with two different contrasts from the same trial.[15] However, according with the inclusion criteria, one of them should not be included. Therefore, it seems reasonable to perform a new systematic review was to compare the efficacy and safety profile of daily vs. intermittent ICS in the management of preschoolers, children and adults with persistent wheezing and mild-to-moderate stable persistent asthma. Two specific questions were identified: 1) Does intermittent therapy with ICS provides significant clinical benefits compared with daily ICS; and 2) What are the risks of daily use of ICS compared with the intermittent-use strategy?

Methods

We adopted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform this systematic review.[16]

Search and selection criteria

We identified published studies from MEDLINE, EMBASE, CINAHL, SCOPUS and the Cochrane Controlled Trials Register (CENTRAL) (April 2013) database using the terms "intermittent" or "as-needed' or "prn" or "irregular" or "sporadic" or "short-course" or "daily" or "regular" or "continuous" and "asthma". Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed.

To be included, studies had to meet all the following criteria: a) randomized (only parallel group) controlled trials without language restriction of more than 8 weeks of duration; b) inclusion of children ($\leq$18 years) and adults with recurrent wheezing or mild to moderate persistent asthma; c) comparison of intermittent or as-needed (intermittent administration of ICS at the onset of exacerbations in combination with rescue SABA) vs. continuous ICS (daily ICS with rescue SABA during exacerbations); long-acting beta2-agonists were excluded as a part of treatment; and d) report at least one of the following outcomes: asthma exacerbations as a primary variable; and pulmonary function tests, symptoms, days without symptoms, SABA use, corticosteroids use, days without rescue medications use, biological markers (eosinophil count in sputum, expired nitric oxide, etc.), withdrawals (total, and due to treatment failure), and serious adverse events (SAE) as secondary variables. A SAE 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.[17]

Data extraction and assessment of risk of bias

Titles, abstracts, and citations were independently analyzed by the two authors (GJR and JCR). From the full text, they 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. Both 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[18] for the following items: 1) adequacy of sequence generation; 2) allocation concealment; 3) blinding of participants and investigators; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective outcome reporting, and other bias. Each potential source of bias was graded as high, low or unclear risk of bias. Disagreements were discussed and resolved by consensus.

Data analysis

Analysis was by intention to treat and included all participants to minimize bias. Outcomes were pooled using mean differences (MDs) (inverse variance method) or Mantel-Haenszel risk ratios (RRs) or hazard ratios (HRs). When effect estimates were significantly different between groups, the number needed to treat for benefit (NNTB) or for harm (NNTH) was obtained. Heterogeneity was measured by the I^2 test[19] ($\leq$25% absence, 26–39% unimportant, 40%–60% moderate, and 60%–100% substantial). Because selected studies differed in the mixes of participants and interventions, a random-effects model was performed to address this variation across studies for all outcomes.[20] As a priori subgroup analysis, we explored the influence of age (children vs. adults), trial duration ($<$54 vs. $\geq$54 weeks) and step-up ICS strategy (equivalent ICS dose in both groups vs. a higher ICS dose in the intermittent group compared to the daily group). Subgroups were compared using the residual Chi^2 test from the Peto odds ratios.[21] Potential publication bias was analyzed through the use of a funnel plot and the Egger test.[22] Inter-observer agreement for full text study selection was measured using kappa statistic. $P \leq 0.05$ (2-tailed test) was considered significant except for the Egger test ($P < 0.1$, and 90% CI). Meta-analysis was performed with the Review Manager 5.2.3 software (Cochrane IMS, 2013).

Results

The process of study selection is outlined in Fig. 1. Reviewer agreement at the level of study selection from full text articles as assessed by kappa statistic was 0.87 (standard error 0.14). Seven trials[8,9,15,23–26] (1367 patients, $\leq$65 years) met the entry criteria. All studies were randomized, parallel group, placebo-controlled, and three[9,23,24] were sponsored by a single pharmaceutical company. Two studies included preschoolers,[24,25] two children,[9,15] and three adults[8,23,26] (Table 1). Most studies included children and adults with mild asthma controlled with low doses of ICS.[8,9,15,23,26] The remaining two studies include preschoolers with a positive asthma predictive index (API)[27] in the first study, and a positive or negative index in the second.[24] In three studies,[9,23,26] the daily ICS dose was stepped-up to the same dose used in the intermittent group. In contrast, four trials[8,15,24,25] compared daily dose to a higher ICS dose in the intermittent group. Beclomethasone or budesonide (160–2000 μg/day) was increased stepwise in the intermittent group for 7–14 days. All studies showed a high adherence to treatment (75%–95%). Overall, the majority of studies were judged to have a low risk of bias (Table 2).

Primary outcome

Data from five studies[8,15,23–25] showed no statistically significant difference in the frequency of asthma exacerbations among patients receiving daily ICS and those receiving intermittent ICS (RR = 0.96; 95% CI, 0.86, 1.06, $p = 0.40$, $I^2 = 0\%$) (Fig. 2A). There was no evidence of publication bias (Egger's test, Intercept = −0.05; 90% CI: −0.31 to 0.68, $p = 0.68$) or significant heterogeneity among studies. In the same way, compared with daily use of ICS, intermittent use of ICS did not significantly decrease the number of patients with one or more exacerbations requiring oral corticosteroids (Fig. 2B). Finally, the pooled analysis did not show a significant difference between groups regarding the time to exacerbation requiring oral corticosteroids, or asthma exacerbations in terms of events/person-year (Table 3). Post hoc subgroup analysis showed no significant differences in terms of age, (RR = 1.23; 95% CI: 0.75, 2.03, $p = 0.4$), duration of studies (RR = 1.4; 95% CI: 0.79, 1.60, $p = 0.46$), or step-up strategy (RR = 1.01; 95% CI: 0.62, 1.63, $p = 0.96$). Sensitivity analysis was not done because the absence of heterogeneity and the high quality of studies.

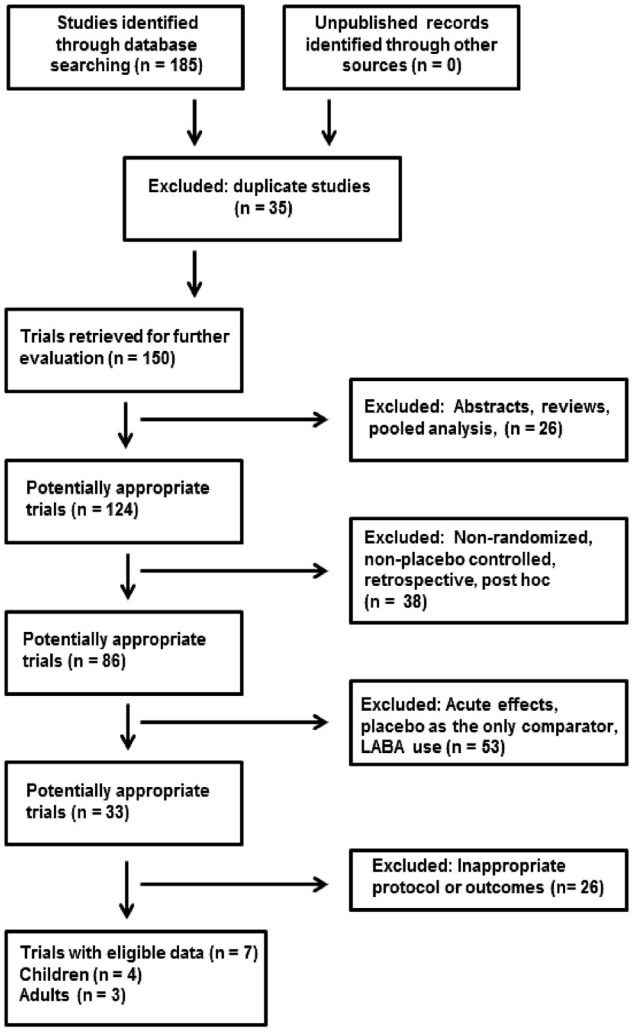

Figure 1 Flowchart for identification of studies used.

Secondary outcomes

Compared to intermittent ICS, the daily ICS group displayed a significant increase in percent asthma-free days (RR = 1.10%; 95% CI: 1.01, 1.20) (Fig. 3A), as well as non-significant decreases in rescue β_2-agonists use (Fig. 3B) and exhaled nitric oxide (Table 3). As was expected, the

Table 1 Characteristics of included studies.[a]

Study	Location and duration, weeks	Randomized patients, *n* (% female)	Mean age, (range)	Eligibility criteria	Primary outcome	Selected comparisons		
						Daily ICS		Intermittent ICS
						Between exacerbations	During exacerbations	
Boushey[8]	Multic 54	149 (62)	33y (18—65)	Physician-diagnosed mild persistent asthma PEF reversibility	Morning PEF	BUD 200 μg TD	BUD 200 μg TD + ALB prn	BUD 400 μg TD for 10 days or PRED 0.5 mg/kg per day for 5days + ALB prn
Papi[23]	Multic 26	234 (58)	37y (18—65	Mild persistent asthma PEF reversibility,	Morning PEF	BDP 250 μg TD	BDP 250 μg TD + ALB 100 μg prn	BDP 250 μg + ALB 100 μg prn
Turpeinen[9]	Single-centre 54	116 (38)	6.9y (5—10)	Interim symptoms PEF reversibility (mild asthma)	Morning PEF	BUD100 μg TD	BUD 400 μg TD for 2 weeks + TERB 0.25 mg/dose prn	BUD 400 μg TD + TERB 0.25 mg/dose for 2 weeks prn
Papi[24]	Multic 12	220 (34)	2.3y (1—4)	Frequent wheezing. API positive or negative	Symptom free days	BDP 400 μg NEB TD	BDP 400 μg NEB TD + ALB 2500 μg prn	BDP 800 μg + ALB 1600 μg prn
Martinez[15]	Multic 44	143 (45)	10.6y (6—18)	Well controlled mild persistent asthma on low dose ICS	Time to first exacerbation.	BDP 40 μg TD	BDP 40 μg TD + ALB prn	BDP 80 μg whenever taking 2 puffs of ALB 180 μg prn
Zeiger[25]	Multic 54	278 (31)	12—53 m (NA)	Recurrent wheezing with API positive values, high-risk asthma and low impairment	Exacerbations	BUD 0.5 mg NEB OD	BUD 0.5 mg NEB OD + ALB 180 μg per MDI or 2.5 mg NEB prn	BUD 1 mg NEB TD for 7days + ALB 180 μg MDI or 2.5 mg NEB
Calhoun[26]	Multic 36 w	227 (68)	33y (NA)	Mild to moderate asthma controlled by low-dose ICS	Time to first treatment failure	BDP 80 μg TD adjusted every 6 w according to guidelines	BDP 80 μg TD adjusted according to guidelines + ALB prn	BDP (80 μg) whenever taking 2 puffs of ALB

[a] ALB = albuterol; API = Asthma predictive index; BDP = beclomethasone; BUD = budesonide; ICS = inhaled corticosteroids; MDI = meter-dose inhaler; Multic = Multicenter; NA = no data available; NEB = nebulized; PEF = peak expiratory flow; PRED = prednisone; OD = once daily; TERB = terbutaline; TD = twice daily.

Table 2 Risk of bias of eligible studies.

Study	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting and other sources of bias
Boushey[8]	Low	Low	Low	Unclear	Low	Low
Papi[23]	Low	Low	Low	Low	Low	Low
Turpeinen[9]	Low	Unclear	Low	Low	Low	Low
Papi[24]	Low	Low	Low	Low	Low	Low
Martinez[15]	Low	Low	Low	Low	Low	Low
Zeiger[25]	Low	Low	Low	Low	Unclear	Low
Calhoun[26]	Low	Low	Low	Low	Low	Low

mean exposure to ICS (beclomethasone or equivalent) was 8.67 mg/monthly less with the intermittent regimen than with the daily regimen (Table 3). One study[8] reported that patients should be treated with daily ICS showing greater improvements in percentage of eosinophils in sputum (MD = 0.50%; 95% CI: 0.45, 0.55, $p = 0.0001$). There were no group differences in pulmonary tests, total withdrawals, withdrawals due to treatment failure, and SAE (Table 3). Finally, pediatric studies did not show significant difference in linear growth rate (MD = 0.35 cm/y; 95% CI: −0.08, 0.78) between groups (Table 3).

Discussion

International guidelines recommend the use of ICS twice daily for people with wheezing and mild-to-moderate persistent asthma to control their condition.[1–3] In addition, patients should use rescue medications when needed to relieve symptoms. However, the daily use of ICS even when people feel fine is very problematic. Thus, many patients tend to take the medication until they become asymptomatic. This pattern of poor adherence to daily use of ICS[28] has led to the hypothesis that linking ICS-use to the intermittent use of a short-acting bronchodilator can improve asthma control, focusing ICS therapy on periods when symptoms are more evident. Additionally, this intermittent-use strategy could potentially reduce costs and adverse events of long-term regular therapy. Thus, the practice of prescribing ICS intermittently was established over a decade ago, although until recently without supporting evidence. It has recently been suggested that as-needed ICS could also be an alternative step-2

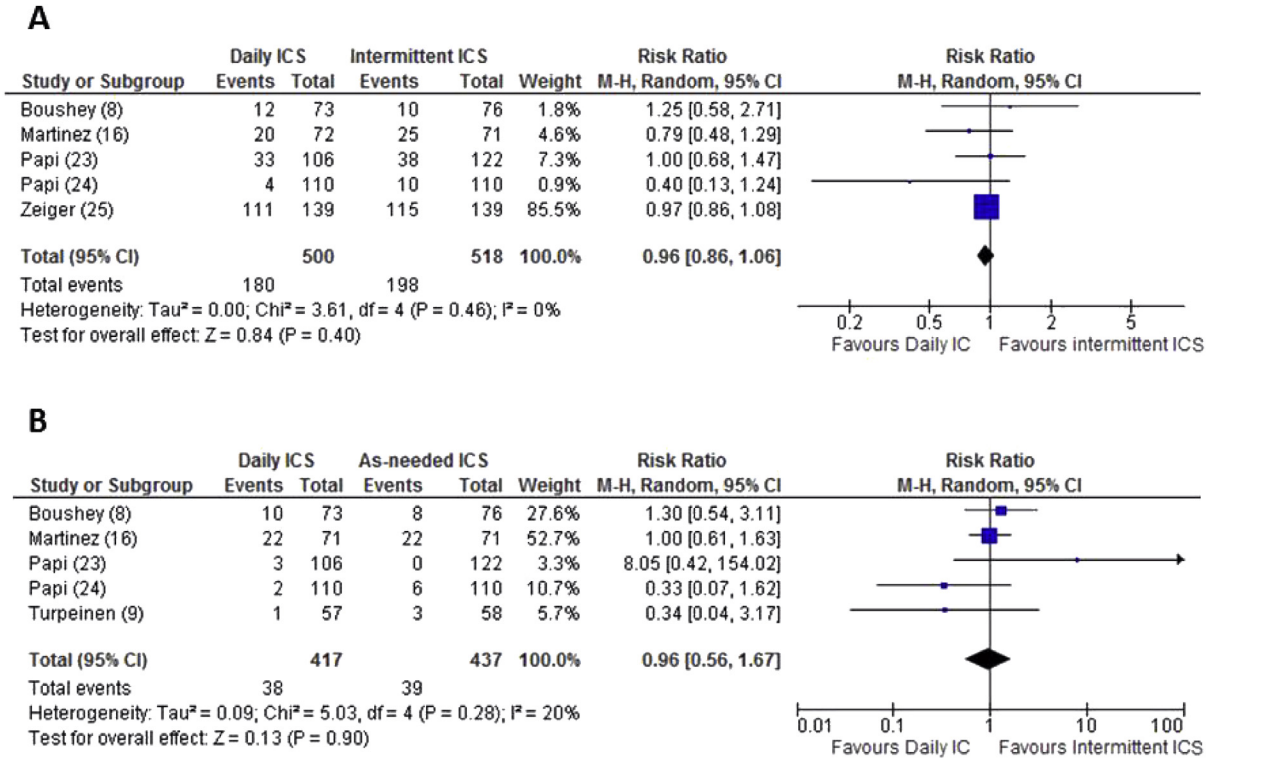

Figure 2 Pooled relative risk for asma exacerbations with 95% confidence intervals of eligible studies comparing daily vs. intermittent ICS use. Rate of exacerbations (Panel A) and number of patients with one or more exacerbations requiring oral corticosteroids (Panel B).

Table 3 Effect of daily vs. intermittent use of ICS on different asthma outcomes.

Outcome	Studies	*n*	Estimate	Effect (95% CI)	I^2 % (p)
Time to exacerbation requiring oral corticosteroids.	15, 25—26	648	HR	1.08 (0.52,2,24)	84 (0.83)
Exacerbations/person-year	23,25—26	733	MD	0.00 (−0.12, 0.13)	0 (0.97)
Mean change exhaled nitric oxide (%).	8,15,26	499	MD	−28.57 (−62.29, 5.14)	59 (0.10)
Cumulative dose of Beclomethasone or equivalent (mg/monthly).	23—26	959	MD	−8.67 (−15.35, −1.98)	96 (0.001)
Mean change pre-bronchodilator FEV_1 (%)	8,15,23,26	851	MD	−0.89 (−2.90, 1.12)	78 (0.39)
Total withdrawals	8,15,23—26	1367	RR	0.93 (0.68, 1.27)	20 (0.65)
Serious adverse events	8—9,15,23—26	1367	RR	0.96 (0.71, 1.30)	0 (0.79)
Withdrawals due to treatment failure	9,15,23,25	771	RR	0.66 (0.23, 1.89)	37 (0.44)
Linear growth rate (cm/y)	9,15,25	537	MD	0.35 (−0.08, 0.78)	0 (0.11)

FEV_1 = forced expiratory volume in the first second; HR = hazard ratio; MD = mean difference; *n* = number of subjects; RR = risk ratio.

therapeutic approach for mild persistent asthma and even for individuals who have not previously received a course of daily corticosteroid treatment.[15]

In the present study, the more extensive systematic review performed exclusively to evaluate the efficacy and safety of intermittent use of ICS compared with daily use in patients with recurrent wheezing and mild to moderate persistent asthma, we did not found significant differences between the two strategies in terms of asthma exacerbations (primary outcome) and pulmonary function tests. Concerning the benefits (first question), daily ICS therapy showed a 10% increase in asthma-free days compared with intermittent-use strategy. Also, daily ICS use was associated with a non-significant decrease in rescue SABA use. However it is difficult to establish the clinical importance of this significant difference. Minimal clinical important differences have rarely been reported for symptom scores, with most papers merely reporting statistically significant changes in mean scores.[29]

About the risks (second question), the daily regimen was associated with greater exposure to ICS. However, there were no significant differences in the rate of total withdrawals, withdrawals due to treatment failure, and SAE. Data from pediatric studies showed a small decline in the short-term linear growth rate during treatment with daily ICS but this effect was not significant. However, this data must be analyzed in light of the fact that the impact on growth is dose dependent. Thus, it is critical to use the

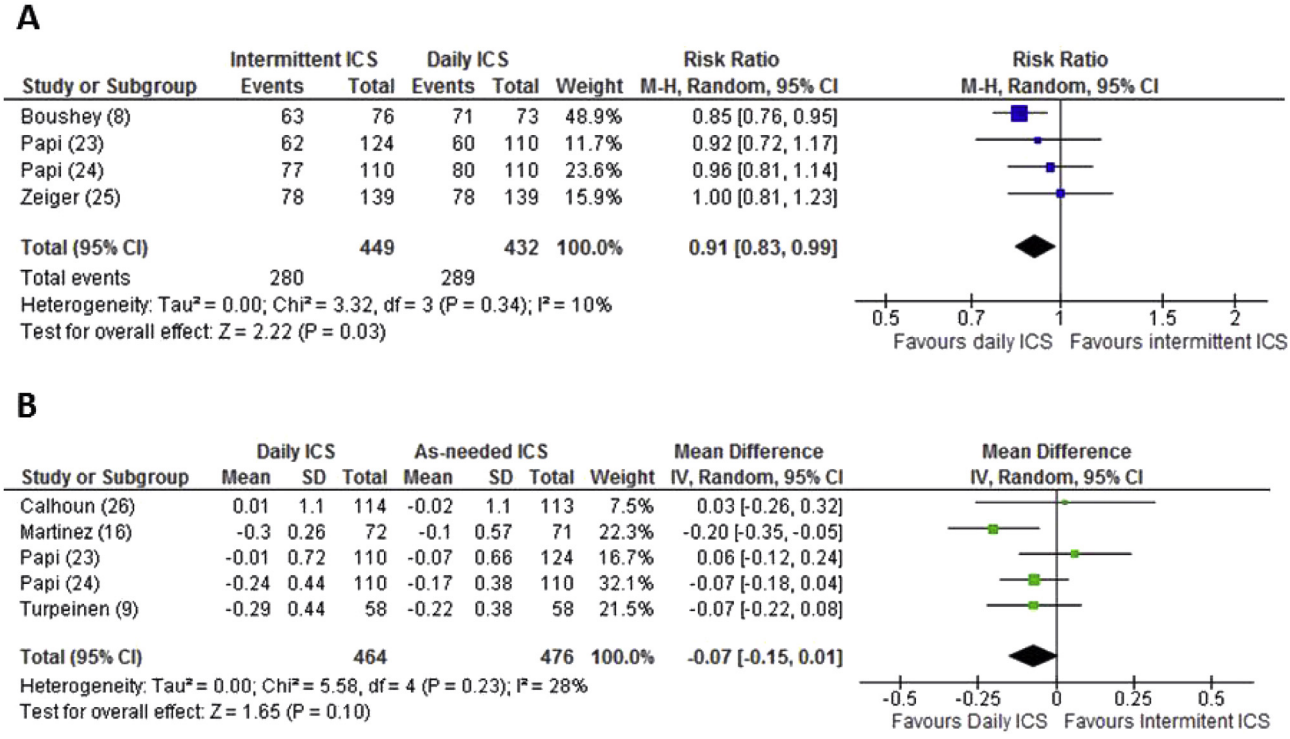

Figure 3 Pooled relative risk for percent asthma free days (Panel A) or mean difference for mean change in rescue medication (Panel B) with 95% confidence intervals of eligible studies comparing daily vs. Intermittent ICS use.

smallest effective dose of ICS (and new safety molecules) and to gradually reduce its use in accordance with clinical follow-up examinations, which was not done in any of the trials included in the present meta-analysis. A recent study reported an initial decrease in attained height associated with the use of ICS (636.1 μg/day of budesonide) in prepubertal children that persisted as a reduction in adult height (1.2 cm), although the decrease was not progressive or cumulative.[30] Finally, of particular concern is the increasing exhaled nitric oxide and eosinophils in sputum associated with the intermittent ICS therapy. More studies are needed evaluating biomarkers and airway remodeling between these two strategies to clarify this issue.

Overall, the results of our systematic review are consistent with those of a previous one.[14] However, both reviews have two important differences. Firstly, Chauhan et al. pooled data from six studies with seven comparisons; authors included two different comparisons from the same trial[15]; however, one of them was excluded in our study according with inclusion criteria (the daily group used ICS plus SABA as rescue medication instead SABA alone). On the other hand, our review included a new trial published in 2012. Together, these differences represent a change of 28% in the sample size between the two studies. Accordingly, this difference may be important due to the small number of studies included, and increases confidence in the results of our review.

This review was performed according to the methodological criteria suggested for scientific guidelines.[16] Trial qualities were formally assessed, and the results were clearly reported; overall, the quality of the studies was high, and there was no evidence of publication bias. Inclusion criteria were clearly defined. Different relevant databases were searched for published and unpublished articles in any language. The effect sizes were consistent and the pooled results of primary outcomes showed homogeneity. Subgroup and sensitivity analysis did not modify the main outcome size effect. However, the small number of trials included can be considered a limitation of this review. As well, the results can be limited by the diversity of the studies related to disease characteristics (wheezing or intermittent or persistent mild asthma).

Does current evidence support a change in the direction of the use of an intermittent-use strategy for recurrent wheezing and mild to moderate persistent asthma? This review suggests a negative answer. Even, some data suggest a slight superiority of the daily-use strategy on the intermittent-use strategy (asthma-free days, rescue medication use, and inflammatory markers). Therefore, at this point, there is no convincing basis to alter the current approach to ICS dosing for mild or mild-to-moderate persistent asthma and more studies are needed comparing these two strategies. While taking in consideration the superiority of daily ICS over intermittent ICS in terms of secondary outcomes, we need to improve patient compliance with daily ICS in order to make asthma control more effective. We should not give up on educating our patients about the favorable risk/benefit balance of daily low-dose ICS simply because it is time-consuming. Instead, we should remember that when recommending intermittent therapy, we are telling our patients that asthma is not a chronic disease, only a recurrent one; so let us be sure, we have classified the phenotype and severity correctly.

In conclusion, this systematic review does not support a change in current guidelines for treatment of recurrent wheezing and mild-to-moderate persistent asthma. Currently, daily ICS is the preferred therapeutic approach.

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Conflict of interests

Dr. Rodrigo has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Almiral, AstraZeneca, Boehringer Ingelheim, Dr. Esteve SA, GlaxoSmithKline, Merck Sharp & Dome, and Novartis. Dr. Castro-Rodriguez Dr. Castro-Rodriguez has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, and Novartis.

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Role of authors.

Dr. Rodrigo: 1) has made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; 2) has drafted the submitted article and revised it critically for important intellectual content, and 3) has provided final approval of the version to be published.

Dr. Castro-Rodriguez: 1) has made substantial contributions to conception, design, and interpretation of data; 2) has revised the article critically for important intellectual content, and 3) has provided final approval of the version to be published.

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