



Daily versus intermittent inhaled corticosteroid treatment for mild persistent asthma

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Purpose of review

Guidelines recommend the use of daily inhaled corticosteroids as preferred treatment for preschoolers, children, adolescents, and adults with recurrent wheezing and mild persistent asthma. However, intermittent or as-needed inhaled corticosteroids treatment in response to symptoms is an emerging strategy. This review is focused on the analysis (clinical efficacy and safety) of this approach in comparison with the current daily-based therapy.

Recent findings

Recently, some authors favored the use of inhaled corticosteroids based on symptoms. It has been suggested that a symptom-based approach could reduce the amount of drug used, minimize the risk of adverse events, and reduce healthcare costs. In contrast, physicians prescribing intermittent inhaled corticosteroids would give the wrong message to their patients about the chronicity of the disease. Currently, there is a significant body of high-quality clinical studies and systematic reviews that have addressed this important controversy, and whose analysis allows us to extract some important conclusions.

Summary

Present evidence does not support a change in the direction of an intermittent or symptom-based use approach for recurrent wheezing and mild-to-moderate persistent asthma. At this point, there is no convincing basis to alter the current strategy to inhaled corticosteroids dosing, and more studies are needed comparing these two approaches.

Keywords

asthma, daily, inhaled corticosteroids, symptom based, treatment

INTRODUCTION

Maintenance or 'proactive' use of low dose of inhaled corticosteroids (ICS) is the most effective therapy to prevent exacerbations and achieve daily asthma control in preschoolers, children, adolescents, and adults with recurrent wheezing and mild persistent asthma [1,2]. In the last decade, the intermittent, symptom-based, or reactive approach has become a very attractive option for asthma patients or parents of children with asthma for different reasons including fear of corticosteroid side-effects, the erroneous concept that the absence of symptoms is equivalent to no disease, and ease of compliance with medications administered for symptoms rather than on a daily basis [3]. Although the assessment of intermittent controller therapy began with adjustable single inhaler therapy in patients with persistent asthma receiving a daily combination of ICS and fast long-acting beta2-agonists in adults and children [4], then this strategy was extended to the use of ICS in adults and children with mild persistent asthma [5,6], and preschoolers

with frequent wheezing [7]. This article is focused on the analysis of symptom-based use of ICS for the treatment of patients with mild persistent asthma and frequent wheezing. Two specific questions were individualized: does intermittent therapy with ICS provides significant clinical benefits compared with daily ICS and what are the risks of daily use of ICS compared with the intermittent-use strategy?

MANAGEMENT OF MILD ASTHMA

Asthma is a clinical syndrome defined by airway inflammation, variable airway obstruction, and hyperresponsiveness [1,2]. Its diagnosis is based

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KEY POINTS

- Guidelines recommend the use of daily ICS as preferred treatment for preschoolers, children, adolescents, and adults with recurrent wheezing and mild persistent asthma.
- Recently, some authors have favored the use of inhaled corticosteroids based on the occurrence of symptoms, suggesting that they could reduce the amount of drug used, minimize the risk of adverse events, and reduce healthcare costs.
- Current evidence does not support a change in the direction of an intermittent or symptom-based use strategy for recurrent wheezing and mild-to-moderate persistent asthma.

on the presence of symptoms of dyspnea, cough, and wheezing, and objective confirmation of variable airflow limitation. Earlier, guidelines classified asthma severity based on the level of symptoms, airflow limitation, and lung function variability in four categories: intermittent, mild, moderate, and severe persistent [8]. However, the main limitation of this method was its poor value in predicting what treatment would be required and what a patient's response to that treatment might be. In view of these limitations, severity is now based on the intensity of treatment required to control the patient's asthma once the diagnosis has been confirmed, comorbidities treated, and inhaler technique and adherence have been optimized [1,9].

Thus, mild asthma is asthma that can be well controlled with regular low intensity treatment such as low-dose ICS, leukotriene modifiers, chromones, or theophylline [1,2]. Of these, use of low-dose ICS therapy on daily basis is recommended as the initial controller treatment for patients of all ages, because they are the most effective medications for achieving treatment goals [10–13]. Also, ICS display superior efficacy to leukotriene modifiers in adults and children with persistent asthma [14,15]. Other options are available but not recommended for routine use as initial or first-line controllers, as they are commonly associated with side-effects or a low efficacy [16].

DAILY VERSUS SYMPTOM-BASED INHALED CORTICOSTEROIDS THERAPY

Emerging evidence over the past decade suggests that other management approaches may provide some advantages to selected patients with asthma, particularly with respect to the question of adjustment of ICS. One such approach is to base the frequency of administration of ICS on the occurrence of

symptoms, in contrast with the predominant approach in which treatment persists independently of ongoing symptoms. The symptom-based approach could reduce the amount of drug used, minimize the risk of adverse events, and reduce healthcare costs. Furthermore, ICS may rapidly exert their anti-inflammatory effects [17], enhance the effect of rescue medications, and be as effective as systemic corticosteroids in treating asthma exacerbations. Concerns about growth retardation, parental resistance, and patient adherence to a daily regimen of ICS promoted this new strategy [18¹,19]. In contrast, physicians prescribing intermittent ICS would give the wrong message to their patients about the chronicity of the disease.

CLINICAL EVIDENCE

A set of high methodological quality studies have been explored by this new approach (Table 1) [5–7, 20–22,23²].

IMPACT study

This was the first study [5] to address the question directly. The trial included adults with a diagnosis of persistent asthma and assessed the hypothesis that symptom-based intermittent treatment of mild asthma would be an acceptable alternative to daily therapy. The three groups received inhaled budesonide, oral zafirlukast, and placebo. All three groups were given a symptom-based action plan that included intermittent ICS, oral corticosteroids, and rescue therapy. The peak expiratory flow in the last 2 weeks at the conclusion of the study (primary outcome) did not differ in the three groups, and no important differences in objective measures of lung function were observed. Differences in the percentage of eosinophils in sputum and exhaled nitric oxide values were seen, favoring individuals treated with daily budesonide compared with treatment with oral zafirlukast or placebo. Asthma-related quality of life assessment was similar in all the groups, but the daily budesonide group also reported better scores on the asthma control score and symptom-free days, as compared with the intermittent group.

Beclomethasone and salbutamol treatment (BEST) study (adults)

This study [20] included adults with mild asthma. It explored the hypothesis that symptom-based therapy with ICS combined with a short-acting beta2-agonist was as effective as daily controller therapy. Patients were assigned to receive: beclomethasone and albuterol in a single inhaler as needed,

Table 1. Summary of randomized clinical trials comparing daily versus intermittent use of inhaled corticosteroids

Author and acronyms	Boushey <i>et al.</i> [5] (IMPACT)	Papi <i>et al.</i> [20] (BEST adults)	Turpeinen <i>et al.</i> [6] (HELSINKI)	Papi <i>et al.</i> [7] (BEST children)	Martinez <i>et al.</i> [21] (TREXA)	Zeiger <i>et al.</i> [22] (MIST)	Calhoun <i>et al.</i> [23**] (BASALT)
Design and duration	Multic randomized, double-blind, parallel group, 54 weeks	Multic randomized, double-blind, parallel group, 6 months	Single center randomized, double-blind, parallel group, 18 months	Multic randomized, double-blind parallel group, 12 weeks	Multic randomized, double-blind, parallel group, 44 weeks	Multic randomized, double-blind parallel group, 52 weeks	Multic randomized, double-blind, parallel group, 9 months
Randomized patients, n (% female)	149 (62)	455 (58)	176 (38)	276 (34)	288 (45)	278 (31)	342 (68)
Age (range)	18–65 years	18–65 years	5–10 years	1–4 years	5–18 years	12–53 months	18–65 years
Asthma severity	Mild	Mild	Mild	Frequent wheezing, API positive or negative	Mild	Frequent wheezing, API positive	Mild-to-moderate asthma
Primary outcome	Morning PEF	Morning PEF	Lung function, exacerbations, and growth	Symptom free days	Time to first exacerbation	Frequency of exacerbations	Time to treatment failure
Interventions	(1) BUD 200 mcg twice daily (2) ZAF 20 mg twice daily (3) BUD 400 mcg twice daily or PRED 5 mg/kg/day during 5 day plus ALB prn (intermittent) (4) BDP 250 mcg twice daily + albuterol 100 mcg twice daily	(1) BDP 250 mcg + ALB as-needed (2) ALB as needed (3) BDP 250 mcg twice daily + ALB as needed (4) BDP 250 mcg twice daily + albuterol 100 mcg twice daily	(1) BUD 400 mcg twice daily for 1 month, 200 mcg twice daily for months 2–6, and 100 mcg twice daily for months 7–18 (2) BUD identical treatment to group 1 during months 1–6, then BUD as-needed for months 7–18 (3) Cromoglycate 30 mg daily for months 1–18	(1) BDP 400 mcg twice daily + ALB prn for months 2–6, and 100 mcg twice daily for months 7–18 (2) BDP 800 mcg + ALB prn (3) ALB prn	(1) BDP 40 mcg HFA twice daily + BDP 40 mcg/ALB as rescue (2) BDP 40 mcg HFA + ALB as rescue (3) ALB as rescue	(1) BUD 0.5 mg once daily + ALB prn (2) BUD 1 mg twice daily for 7 days + ALB prn (3) BDP (80 mcg) whenever taking two puffs of ALB	(1) BDP 80 mcg twice daily adjusted every 6 weeks according to guidelines (2) BDP 80 mcg twice daily adjusted according to guidelines + ALB prn

ALB, albuterol; API, asthma predictive index; BDP, beclomethasone; BUD, budesonide; ICS, inhaled corticosteroids; MDI, meter-dose inhaler; Multic, multicenter; PRED, prednisone; ZAF, zafirlukast.

albuterol as needed, regular beclomethasone, and regular beclomethasone and albuterol in a single inhaler. The morning peak expiratory flow rate during the last 2 weeks of the 6-month treatment (primary outcome) was higher, and the number of exacerbations was lower in the as-needed combination therapy group than in the as-needed albuterol therapy group, but the values in the as-needed combination therapy group were not significantly different from those in the groups receiving regular beclomethasone therapy or regular combination therapy.

Helsinki early intervention childhood study

This study [6] included children categorized as having mild persistent asthma. It was designed to evaluate the efficacy and safety of daily versus as-needed budesonide. Patients were assigned to three treatment groups: continuous budesonide (400 mcg twice daily for the first month, then 200 mcg twice daily for 5 months) followed by low-dose budesonide (100 mcg twice daily for 12 months); budesonide group, in which patients received identical budesonide treatment as Group 1 for the first 6 months followed by budesonide for exacerbations as-needed for months 7–18; and a control group in which patients received disodium cromoglycate for 18 months. Compared with cromoglycate, regular budesonide treatment resulted in a significantly improved lung function, fewer exacerbations, and a small but significant decline in growth velocity (primary outcomes). After 18 months, however, the lung function improvements did not differ between the groups. During months 7–18, patients receiving continuous budesonide treatment had significantly fewer exacerbations compared with groups 2 and 3. The number of asthma-free days did not differ between regular and intermittent budesonide treatment. Growth velocity was normalized during continuous low-dose budesonide and budesonide therapy given as needed. The latter was associated with catch-up growth. Regular use of budesonide gave better asthma control but had a more systemic effect than did use of budesonide as needed.

Beclomethasone and salbutamol treatment (BEST) study (children)

The authors conducted a trial to determine whether regular nebulized glucocorticoid and a bronchodilator (as-needed) or the simple as-needed use of a nebulized bronchodilator/glucocorticoid combination and no regular treatment was more effective than an as-needed bronchodilator alone in preschool children with frequent wheezing [7]. Patients were assigned to one of three

groups: regular beclomethasone and salbutamol as-needed, beclomethasone and salbutamol as-needed, and salbutamol as-needed. Treatment with regular beclomethasone increased the percentage of symptom-free days (primary outcome) and improved several important secondary outcomes, including exacerbations compared with as-needed salbutamol. On the other hand, as-needed combination was not statistically superior to as-needed salbutamol although not different from regular beclomethasone on the primary outcome.

Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA) study

The study [21] included children with mild persistent asthma. The goals of this study were to establish whether discontinuation of daily inhaled corticosteroids in children with well controlled, mild persistent asthma is associated with an increased risk of exacerbations, and whether or not the use of beclomethasone plus albuterol for relief, with or without concomitant use of daily beclomethasone, provides better protection against exacerbations than does a rescue strategy that uses albuterol alone. Patients were assigned to: daily beclomethasone with beclomethasone and albuterol as needed; daily beclomethasone and albuterol as rescue, beclomethasone and albuterol as rescue, and albuterol as rescue. The hazard ratio for asthma exacerbations (primary outcome) was lower in patients using albuterol and beclomethasone on a symptom-driven basis, compared with placebo-treated patients, but the difference did not achieve statistical significance. In contrast to using daily ICS, the beclomethasone/albuterol rescue group had less protection against exacerbations. The authors suggested that rescue beclomethasone can lower risk of asthma exacerbations, but its effect was less than daily ICS. Using growth in height as one of the surrogates for side-effects of long-term ICS exposure, the investigators found that children on daily ICS had approximately 1 cm less growth as compared with the placebo group, and children using ICS as rescue had comparable heights to the placebo-treated children. However, there was an increase in fractional exhaled nitric oxide (FENO), beginning at week 8, in individuals in the rescue beclomethasone and placebo groups compared with placebo and daily beclomethasone groups.

Maintenance and intermittent inhaled corticosteroids in wheezing toddlers study (MIST)

This trial included preschoolers who had positive values on the modified asthma predictive index,

along with recurrent wheezing, high-risk asthma, and low impairment (infrequent use of albuterol and infrequent night awakenings between episodes) [22]. The aim was to determine whether a daily low-dose regimen of budesonide would be superior to an intermittent high-dose regimen. Children were assigned to receive a budesonide inhalation suspension for 1 year as either an intermittent high-dose regimen, or a daily low-dose regimen. The daily regimen of budesonide did not differ significantly from the intermittent regimen with respect to the frequency of exacerbations (primary outcome). There were also no significant between-group differences in several other measures of asthma severity, including the time to the first exacerbation, or adverse events.

Symptom-based strategies for adjustment of inhaled corticosteroid therapy study (BASALT)

The authors tested the hypothesis if adjustment of ICS therapy based on FENO or day-to-day symptoms is superior to guideline-informed, physician assessment-based adjustment in preventing treatment failure in adults with mild-to-moderate asthma [23²⁴]. Individuals were assigned to three groups in which adjustment of daily ICS use was based on physician assessment of lung function, symptoms, and rescue albuterol use (guideline-based adjustment), FENO (biomarker-based adjustment), and beclomethasone and albuterol as needed. There were no significant differences among the three strategies in time to treatment failure (primary outcome). Additionally, no difference in asthma exacerbation rates and proportion of treatment failures progressing to exacerbations were identified among groups.

SYSTEMATIC REVIEWS

In order to clarify the results, two systematic reviews have examined the information available from clinical trials using the meta-analysis technique [24²⁵]. The first was a Cochrane review that compared the efficacy and safety of intermittent versus daily ICS in the management of children and adults with persistent asthma and preschool-aged children suspected of persistent asthma [24²⁵]. The search of literature was conducted until December 2011, and the authors included six studies with seven comparisons. There was no statistically significant group difference in the risk of patients experiencing exacerbations requiring oral corticosteroids [1204 patients; risk ratio = 1.07; 95% confidence interval (CI): 0.87–1.32]. No group difference

was observed in the risk of patients with serious adverse events (1055 patients; risk ratio = 0.82; 95% CI: 0.33–2.03). Compared with the daily ICS group, the intermittent ICS group displayed a smaller improvement in change from baseline peak expiratory flow rate, fewer symptom-free days, fewer asthma control days, more use of rescue medication, and a greater increase from baseline in exhaled nitric oxide. There was no significant group difference in pulmonary function, quality of life, airway hyperreactivity, adverse events, hospitalizations, emergency department visits, or withdrawals. In pediatric trials, intermittent ICS were associated with greater growth by 0.41 cm change from baseline (532 children; 95% CI: 0.13–0.69) compared with daily treatment.

More recently, Rodrigo and Castro-Rodriguez [25²⁶] published a second systematic review on the same topic updated to April 2013. Seven trials (1367 patients) met the entry criteria. 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 (risk ratio = 0.96; 95% CI: 0.56–1.57). Also, the daily ICS group displayed a significant increase in percentage asthma-free days (569 patients, risk ratio = 1.10; 95% CI: 1.01–1.20) as well as nonsignificant decreases in rescue medication use and exhaled nitric oxide. There were no group differences in pulmonary tests, total withdrawals, withdrawals because of treatment failure, and serious adverse events. Pediatric studies did not show significant difference in linear growth rate (537 patients, mean difference = 0.35 cm/year; 95% CI: –0.08 to 0.78) between groups.

CONCLUSION

Daily use of ICS even when people feel fine is problematic, because many patients tend to take the medication until they become asymptomatic. This pattern of poor adherence to daily use of ICS 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 [19]. Also, this strategy could potentially reduce costs and adverse events of long-term regular therapy. Therefore, it has recently been suggested that as-needed ICS could also be an alternative therapeutic approach for mild persistent asthma and even for individuals who have not previously received a course of daily corticosteroid treatment [21].

With respect to our initial questions, the evidence suggests that compared with daily ICS therapy, the symptom-based approach displayed

a smaller improvement in change from baseline peak expiratory flow rate, fewer symptom-free days, fewer asthma control days, more use of rescue medication, and a greater increase from baseline in exhaled nitric oxide. About the risks, the daily regimen was associated with greater exposure to ICS. However, there were no significant differences in the rate of total withdrawals, withdrawals because of treatment failure, and severe adverse events. 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. Finally, of particular concern was the increasing exhaled nitric oxide and eosinophils in sputum associated with the intermittent ICS therapy. Asthma is an inflammatory disease of the airways, and this inflammation is not only present during exacerbations or when the patient has symptoms but persists for very long periods, possibly throughout life. More information is needed evaluating biomarkers and airway remodeling between these two strategies.

Current evidence does not support a change in the direction of an intermittent or symptom-based use strategy for recurrent wheezing and mild-to-moderate persistent asthma. At this point, there is no convincing basis to alter the current approach to ICS dosing, and more studies are needed comparing these two strategies. While taking in consideration the superiority of daily ICS over intermittent ICS in terms of some outcomes, we need to improve patient compliance with daily ICS in order to make asthma control more effective. We should remember that when recommending symptom-based therapy, we are telling our patients that asthma is not a chronic disease, only a recurrent one.

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Conflicts of interest

No sponsorship from institutions or the pharmaceutical industry was provided to conduct this study. Dr Rodrigo reports receiving consulting and lecture fees from Air Products, Boehringer Ingelheim, GlaxoSmithKline, Novartis, GlaxoSmithKline, and Chiesi.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Update 2011. Available on http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf. [Accessed December 9, 2013]
2. National Asthma Education and Prevention Program Expert Panel Report 2 (1997) Guidelines for the diagnosis and management of asthma. Bethesda: National Heart, Lung, and Blood Institute.
3. Ducharme FM. Continuous versus intermittent inhaled corticosteroids for mild persistent asthma in children: not too much, not too little. *Thorax* 2012; 67:102–105.
4. O'Byrne PM, Bisgaard H, Godard PP, *et al.* Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005; 171:129–136.
5. Boushey HA, Sorkness CA, King TS, *et al.* Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005; 352:1519–1528.
6. Turpeinen M, Nikander K, Pelkonen AS, *et al.* Daily versus as-needed inhaled corticosteroid for mild persistent asthma (The Helsinki early intervention childhood asthma study). *Arch Dis Child* 2008; 93:654–659.
7. Papi A, Nicolini G, Baraldi E, *et al.* Regular vs. prn nebulized treatment in wheeze preschool children. *Allergy* 2009; 64:1463–1471.
8. Global Initiative for Asthma. Workshop report. Global strategy for asthma management and prevention 2002.
9. Taylor DR, Bateman ED, Boulet L-P, *et al.* A new perspective on concepts of asthma severity and control. *Eur Respir J* 2008; 32:545–554.
10. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, *et al.* Low dose inhaled budesonide in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001; 164:1392–1397.
11. Adams NP, Bestall JC, Malouf R, *et al.* Beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev* 2005; 1: CD002738.
12. Busse WW, Pedersen S, Pauwels RA, *et al.* The inhaled steroid treatment as regular therapy in early asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol* 2008; 121:1167–1174.
13. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009; 123:519–525.
14. Castro-Rodriguez JA, Rodrigo GJ. The role of inhaled corticosteroids and montelukast in children with mild–moderate asthma: results of a systematic review with meta-analysis. *Arch Dis Child* 2010; 95:365–370.
15. Chauhan BF, Ducharme FM. Antileukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev* 2012; 5: CD002314.
16. Dennis RJ, Solarte I, Rodrigo G. Asthma in adults. *Clin Evid* 2011; 1512.
17. Rodrigo GJ. Comparison of inhaled fluticasone with intravenous hydrocortisone in the treatment of adult acute asthma. *Am J Respir Crit Care Med* 2005; 171:1231–1236.
18. Kelly HW, Sternberg AL, Lescher R, *et al.* Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012; 367:904–912.
This study analyzed the effect of inhaled glucocorticoids in childhood on adults height (9.1 years of follow-up), until the ages of 12–23 years.
19. Williams LK, Peterson EL, Wells K, *et al.* Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol* 2011; 128:1185–1191.
20. Papi A, Canonica GW, Maestrelli P, *et al.* Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007; 356:2040–2052.
21. Martinez FD, Chinchilli VM, Morgan WJ, *et al.* Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377:650–657.
22. Zeiger RS, Mauger D, Bacharier LB, *et al.* Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011; 365:1990–2001.
23. Calhoun WJ, Ameredes BT, King TS, *et al.* Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012; 308:987–997.
Among adults with mild-to-moderate persistent asthma, the use of either biomarker-based or symptom-based adjustment of inhaled corticosteroids was not superior to physician assessment-based adjustment of inhaled corticosteroids in time to treatment failure.
24. Chauhan BF, Chartrand C, Ducharme FM. Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. *Cochrane Database Syst Rev* 2012; 12:CD009611; DOI: 10.1002/14651858.CD009611.pub2.
Cochrane systematic review that showed that daily ICS was superior to intermittent ICS in lung function, airway inflammation, asthma control and reliever use.
25. Rodrigo GJ, Castro-Rodriguez JA. Daily vs. intermittent inhaled corticosteroids for recurrent wheezing and mild persistent asthma: a systematic review with meta-analysis. *Respir Med* 2013; 107:1133–1140.
Independent systematic review whose results suggests to not change daily for intermittent inhaled corticosteroids use among preschoolers, children with persistent wheezing, and adults with mild-to-moderate stable persistent asthma.