

Continuous versus intermittent inhaled corticosteroids for mild persistent asthma in children: not too much, not too little

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The goal of asthma treatment is to prevent exacerbations, achieve daily asthma control and prevent adverse effects with a minimum of medication. In preschoolers, children and adolescents with mild persistent asthma, the most effective therapy remains daily use of low-dose inhaled corticosteroids.¹ Why then consider intermittent therapy over maintenance inhaled corticosteroids?

The intermittent approach is attractive to patients and families for a variety of reasons, including fear of corticosteroid side effects,² the erroneous concept that no symptoms equate to no disease³ and ease of compliance with medications administered for symptoms rather than on a daily basis. Indeed, pharmacy records clearly show that most children with asthma infrequently renew their prescriptions for controller medications, suggesting that they may not understand, perceive or agree with the need for daily therapy, despite ongoing healthcare resources utilisation and excess use of rescue β_2 -agonist.⁴

This practice is also endorsed by physicians who recommend an asthma controller at the onset of an exacerbation for a short period.^{4, 5} In vogue since the 1990s without, until recently, any supporting evidence, the practice of prescribing intermittent therapy over continuous therapy may have stemmed from: (1) the uncertain benefit of daily inhaled corticosteroids in patients in whom there is diagnostic uncertainty (viral wheeze vs asthma), phenotype hesitation (intermittent vs persistent) or

a paucity of evidence for therapy (eg, preschoolers); (2) conflicting evidence regarding the long-term benefit of daily therapy as a disease modifier (eg, lung function, quality of life, airway remodelling)^{6–8}; (3) concerns about side effects of daily inhaled corticosteroids; and (4) in the absence of trials, unconvincing evidence of the harm or lack of efficacy of intermittent therapy. Admittedly, these factors may contribute to the ‘giving-up to poor compliance’ popular approach to avoid the time and energy required to repeatedly convince patients that the benefits of daily therapy outweigh possible harms.^{2, 9, 10} These reasons must be carefully addressed.

The scientific evaluation of intermittent controller therapy has started with adjustable single inhaler therapy in patients with persistent asthma receiving a daily combination of inhaled corticosteroids and fast long-acting β_2 -agonists (ie, formoterol) in adults,^{11, 12} then in children.¹³ It extended to patients with intermittent asthma on no maintenance controller in whom placebo-controlled trials examined ‘as-needed’ combination therapy in adults¹⁴ and ‘as-needed’ inhaled corticosteroids^{15, 16} or leukotriene receptor antagonists¹⁷ monotherapy in children. The recent randomised control trials testing intermittent versus continuous controller monotherapy in adults^{18, 19} and children^{20, 21} with mild persistent asthma are the focus of this commentary.

In a 6-month, three-arm trial, Boushey *et al* evaluated as needed budesonide (800 $\mu\text{g}/\text{day}$ for 10 days) in adults with mild persistent asthma who were taking 400 μg daily budesonide or placebo; they observed no significant group difference in morning peak expiratory flow (PEF) rate and in exacerbations.¹⁸ However, maintenance monotherapy was clearly superior in improving forced expiratory volume in one second (FEV₁), airway hyper-reactivity, asthma control, symptom-free days and markers of eosinophilic inflammation.

Intermittent budesonide was no different from daily zafirlukast and the authors appropriately emphasised the need for further studies before endorsement.¹⁸ In a 6-month, four-arm trial, Papi and colleagues evaluated daily 100 μg of hydrofluoroalkane (HFA)-beclomethasone versus as needed two puffs of 50 μg of HFA-beclomethasone dipropionate (BDP) and 100 μg salbutamol combined in a single inhaler. There was no significant group difference in morning PEF, exacerbations, symptoms and rescue β_2 -agonists use; thus, the authors concluded that both strategies were equivalent.¹⁹ The evidence in paediatrics is also limited to two trials, but several ongoing studies will shed more light on the topic in the near future (NCT00675584; NCT00394329). Turpeinen and colleagues designed an 18-month, 3-arm randomised controlled trial to carefully examine the efficacy and the safety profile of intermittent therapy in children with newly diagnosed asthma (mean baseline FEV₁ of 85% of the predicted value).²⁰ All groups received rescue 800 $\mu\text{g}/\text{day}$ of budesonide for 10 days and rescue terbutaline for exacerbations. After 6 months of identical therapy with 800 $\mu\text{g}/\text{day}$ of budesonide for 1 month and 400 μg for 5 months, daily low-dose (200 $\mu\text{g}/\text{day}$) budesonide was associated with 60% fewer exacerbations and fewer withdrawals due to exacerbations requiring rescue oral corticosteroids than the intermittent group. There was no significant difference in symptom-free days, morning PEF and FEV₁, although for several variables the values for the intermittent group were intermediate between that of daily budesonide and cromoglycate. Finally, Martinez and colleagues examined in children with persistent asthma (mean baseline FEV₁ of 100% of the predicted value), daily 100 μg of HFA-beclomethasone versus as-needed 100 μg of HFA-beclomethasone combined with 200 μg salbutamol in a single inhaler.²¹ There was no group difference between daily and as-needed beclomethasone in any outcomes, with the exception of expired nitric oxide, which was significantly lower throughout the study for daily beclomethasone. How does one reconcile these findings?

In an emerging field of a new therapy, the absence of group difference in certain outcomes always raises the issue as to whether the findings are evidence of no effect (real equivalence) or no evidence of effect (lack of power). Giving the size of the confidence intervals, the latter is at play for several outcomes. This issue

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of statistical power could be overcome by comparing thousands of patients in a new multicentre trial or easier, in a meta-analysis of several randomised controlled trials, such as the one currently in progress with the Cochrane Collaboration. There is also the possibility that patient selection, outcome selection and treatment modalities may affect the findings. Perhaps the most important issue is the accuracy of the phenotype, that is, whether the trials adequately distinguished intermittent from mild persistent asthma. Indeed, one would expect intermittent and daily therapy to work equally well in patients with intermittent asthma, erroneously classified as persistent asthma, because daily therapy would represent overtreatment. The outcomes of interest must be relevant for the level of control, while avoiding the common pitfall of selecting variables with a ceiling effect, that is, variables that are normal or near normal at baseline, such as lung function and rescue β_2 -agonist use, as they require more power to identify as statistically significant differences that may not be clinically important. Selecting exacerbations as an outcome is attractive, as these events may be eventually relevant to most patients, although longer study durations are needed to allow for occurrence of sufficient events in patients with good control at baseline. Could differences in patient phenotypes, baseline asthma control, selection of outcomes and type and duration of interventions account for the apparent discordance in findings?

Clearly, in half of the trials, daily inhaled corticosteroid was superior to intermittent therapy, which in turn was superior to placebo for preventing exacerbations. In these patients, the intermediate efficacy of intermittent therapy is in line with prior observations that, at equal severity, greater compliance to daily controller is associated with better asthma control in patients with persistent asthma.^{22–25} The paediatric study reporting group difference only in expired nitric oxide had selected children with superior lung function, raising the possibility that a substantial proportion has intermittent mild asthma.

What about safety? The search for adverse effects has been minimal so far in adults, but rather extensive in the two paediatric studies. Six-month therapy with high and moderate doses of budesonide was associated with an estimated growth suppression of 2 cm/year compared with those on cromoglycate.

This was followed by normal and even perhaps a catch-up growth in the last 12 months and minor decrease in skin thickness, with no group difference in bone mineral density and intraocular pressure compared with cromoglycate. Although height velocity in the last 12 months was significantly greater by 0.6 cm in the intermittent group, compared with the daily budesonide groups, there was no significant difference in the final height attained, suggesting that the major impact on growth occurred in the initial 6 months. Similarly, in the second paediatric trial, the daily beclomethasone group grew 0.7 cm less than the intermittently treated group.²¹ The readers are left with the conclusion that one must choose between better control with stunted growth using daily inhaled corticosteroids or more exacerbations with normal growth using intermittent corticosteroids.

However, this paradigm must be rephrased for two reasons. First, because the impact on growth is dose dependent, it is critical to use the smallest effective dose of inhaled corticosteroids and taper it according to control, which was not done in any of the four trials. In the study by Turpeinen and colleagues, the use of high and moderate doses probably resulted in overtreatment for the majority of children enrolled, as most were subsequently well controlled on low-dose budesonide. Second, the growth suppression is drug dependent with group differences of 1.51 cm/year with 400 $\mu\text{g}/\text{day}$ of beclomethasone, 1.0 cm/year with 200 $\mu\text{g}/\text{day}$ of budesonide and 0.43 cm/year with 200 $\mu\text{g}/\text{day}$ of fluticasone.^{26–27} The data on ciclesonide has shown no systemic effect to date, including no detectable effect on growth.^{28–29} Consequently, there is little reason to accept the known risk of growth suppression associated with beclomethasone or budesonide, when safer inhaled corticosteroids may be used.

How can we move this field forward? Clearly, in view of the expected between-physician variability in phenotype ascertainment, we urgently need to validate the criteria recently proposed by several paediatric groups to distinguish intermittent from persistent asthma in preschoolers as well as in school-aged children and adolescents.^{30–32} It appears worthwhile to consider adding an objective measure of lung function (including interrupter technique or oscillometry in preschool-aged children who are too young to undergo spirometry) and inflammatory markers (eg, expired nitric oxide) to

improve accuracy and reduce subjectivity in phenotype classifications.^{33–34} With increasing evidence that even with minimal symptoms, people with intermittent asthma display ongoing inflammation, should there be a distinction between mild intermittent and mild persistent asthma? Before adding intermittent therapy as a therapeutic option in our guidelines, we should ensure that we are not causing harm and diligently compare the long-term impact of both strategies on exacerbations, lung growth and function, quality of life and airway remodelling.

In summary, there is insufficient evidence to recommend intermittent therapy in patients with persistent asthma. Half of the published trials testing intermittent versus low-dose continuous inhaled corticosteroids confirmed the superiority of daily low-dose, over intermittent, inhaled corticosteroids, and the latter over placebo; this is entirely consistent with—the better the compliance with daily use of inhaled corticosteroids, the better the asthma control. We should not give up educating our patients about the favourable risk–benefit balance of low-dose inhaled corticosteroids, simply because it is time-consuming, no more than we should abandon recommending tobacco avoidance, bicycle helmets and car seats. In patients with superior lung function, longer trials are needed before assuming equivalence, as the delay until recurrence of symptoms and exacerbation should be proportional to baseline control and the rapidity of inflammatory build-up. In addition, long-term trials demonstrating the safety of intermittent therapy compared with daily therapy on lung function and airway remodelling must be conducted to ensure that we are not causing harm in these future young adults. One must remember that adverse effects of inhaled corticosteroids are dose dependent and appear to be drug dependent. Until we have more data, it seems that the best approach for children with mild persistent asthma remains inhaled corticosteroids at the lowest effective dose, using the safest molecules. When recommending intermittent therapy, we are telling our patients that asthma is not a chronic disease, only a recurrent one; let us be sure, we have classified the phenotype correctly.

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REFERENCES

- Guilbert TW**, Morgan WJ, Zeiger RS, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *New Engl J Med* 2006;**354**:1985–97.
- Rabe KF**, Adachi M, Lai CK, *et al.* Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;**114**:40–7.
- Halm EA**, Mora P, Leventhal H. No symptoms, no asthma: the acute episodic disease belief is associated with poor self-management among inner-city adults with persistent asthma. *Chest* 2006;**129**:573–80.
- Pando S**, Lemièrè C, Beauchesne MF, *et al.* Suboptimal use of inhaled corticosteroids in children with persistent asthma: inadequate prescription, poor drug adherence, or both? *Pharmacotherapy* 2010;**30**:1109–16.
- Blais L**, Kettani FZ, Lemièrè C, *et al.* Inhaled corticosteroids vs. leukotriene-receptor antagonists and asthma exacerbations in children. *Respir Med* 2011;**105**:846–55.
- Agertoft L**, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;**88**:373–81.
- Montuschi P**, Pagliari G, Fuso L. Pharmacotherapy of asthma: regular treatment or on demand? *Ther Adv Respir Dis* 2009;**3**:175–91.
- Murray CS**. Can inhaled corticosteroids influence the natural history of asthma? *Curr Opin Allergy Clin Immunol* 2008;**8**:77–81.
- Cabana MD**, Abu-Isa H, Thyne SM, *et al.* Specialty differences in prescribing inhaled corticosteroids for children. *Clin Pediatr (Phila)* 2007;**46**:698–705.
- Johnston NW**, Johnston SL, Duncan JM, *et al.* The September epidemic of asthma exacerbations in children: a search for etiology. *J Allergy Clin Immunol* 2005;**115**:132–8.
- 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**:129–36.
- Rabe KF**, Atienza T, Magyar P, *et al.* Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;**368**:744–53.
- Bisgaard H**, Le Roux P, Bjamer D, *et al.* Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006;**130**:1733–43.
- Haahntela T**, Tamminen K, Malmberg LP, *et al.* Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: A SOMA study. *Eur Respir J* 2006;**28**:748–55.
- Bisgaard H**, Hermansen MN, Loland L, *et al.* Intermittent inhaled corticosteroids in infants with episodic wheezing. *New Engl J Med* 2006;**354**:1998–2005.
- Ducharme FM**, Lemire C, Noya FJ, *et al.* Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;**360**:339–53.
- Robertson CF**, Price D, Henry R, *et al.* Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;**175**:323–9.
- Boushey HA**, Sorkness CA, King TS, *et al.* Daily versus as-needed corticosteroids for mild persistent asthma. *New Engl J Med* 2005;**352**:1519–28.
- 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**:2040–52.
- 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**:654–9.
- 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**:650–7.
- Adams RJ**, Fuhlbrigge A, Finkelstein JA, *et al.* Impact of inhaled antiinflammatory therapy on hospitalization and emergency department visits for children with asthma. *Pediatrics* 2001;**107**:706–11.
- Mudd K**, Bollinger ME, Hsu VD, *et al.* Pharmacy fill patterns in young urban children with persistent asthma. *J Asthma* 2006;**43**:597–600.
- Walders N**, Kopel SJ, Koinis-Mitchell D, *et al.* Patterns of quick-relief and long-term controller medication use in pediatric asthma. *J Pediatr* 2005;**146**:177–82.
- Suissa S**, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;**57**:880–4.
- Sharek PJ**, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. *Pediatrics* 2000;**106**:E8.
- The Childhood Asthma Management Program Research Group**. Long-term effects of budesonide or nedocromil in children with asthma. *New Engl J Med* 2000;**343**:1054–63.
- Von Berg A**, Engelstatter R, Minic P, *et al.* Comparison of Ciclesonide 160ug/d with Budesonide 400ug/d in a Randomised Double-blind Study in Children with Moderate to Severe Asthma. *Pediatr Allergy Immunol* 2007;**18**:391–400.
- Skoner DP**, Maspero J, Banerji D, *et al.* Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. *Pediatrics* 2008;**121**:e1–14.
- Bacharier LB**, Boner A, Carlsen KH, *et al.* Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;**63**:5–34.
- Brand PL**, Baraldi E, Bisgaard H, *et al.* Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;**32**:1096–110.
- Gastro-Rodríguez JA**, Holberg CJ, Wright AL, *et al.* A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;**162**:1403–6.
- Beydon N**, Davis SD, Lombardi E, *et al.* An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* 2007;**175**:1304–45.
- Bacharier LB**. Does exhaled nitric oxide measurement help distinguish between wheezing phenotypes in preschool children? *J Allergy Clin Immunol* 2008;**121**:710–11.