

Treatment of mild persistent asthma in children

Fernando Martinez and co-workers (Feb 19, p 650)¹ highlight that daily use of inhaled corticosteroids is associated with reduced growth, and that intermittent use of these drugs to control mild persistent asthma avoids such growth impairment. This statement could lead physicians and (parents of) patients to think that daily inhaled corticosteroid treatment is unsafe and stunts growth. I would like to point out that the currently available evidence does not support a clinically relevant effect on long-term growth of inhaled corticosteroid therapy in children.

The effects of inhaled corticosteroids on growth have been extensively studied and reviewed.² Although low to moderate doses (<400 µg per day budesonide or equivalent) are associated with a reduction of growth in height during the first year of treatment of 1–2 cm, this effect does not accumulate over further years of treatment.³ Studies that have followed up children on inhaled corticosteroids for many years into adulthood consistently show normal adult attained height,⁴ probably because these children grow for longer than their peers and reach normal adult height at a slightly later age.⁵ Thus, inhaled corticosteroids seem to reset the growth clock temporarily, after which normal growth recurs and remains.

In my opinion, it is therefore inappropriate to use the expected slight growth reduction in the first year of inhaled corticosteroid treatment as an argument against long-term maintenance treatment with such drugs, because the long-term growth of children who use these compounds for many years is normal.

I declare that I have no conflicts of interest.

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- 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**: 650–57.
- Leone FT, Fish JE, Szefer SJ, West SL. Systematic review of the evidence regarding potential complications of inhaled corticosteroid use in asthma: collaboration of American College of Chest Physicians, American Academy of Allergy, Asthma, and Immunology, and American College of Allergy, Asthma, and Immunology. *Chest* 2003; **124**: 2329–40.
- Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; **343**: 1054–63.
- Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000; **343**: 1064–69.
- Pedersen S. Do the benefits of daily inhaled steroid treatment of mild asthma outweigh the risks? *Arch Dis Child* 2008; **93**: 644–45.

In their randomised controlled study of children with mild persistent asthma, Fernando Martinez and colleagues¹ show that regular inhaled steroids plus use of combined inhaled steroids plus salbutamol for rescue use is best at reducing and preventing exacerbations (measured by treatment failure). They conclude that “the most effective treatment to prevent exacerbations is daily inhaled corticosteroids”. However they, and in his accompanying Comment, William Checkley,² imply that inhaled corticosteroids as rescue medication with albuterol/salbutamol might be useful for treating these children.

Although this rescue approach is a concept that has become accepted and criticised³ after studies in adults using the so called Symbicort SMART Regime,⁴ the suggestion that this form of treatment might be useful in children is worrying, because of Martinez and colleagues' findings. Although, compared with placebo, there were fewer exacerbations and episodes of “treatment failure” in the rescue group, the bottom line is that more than a third of patients prescribed the rescue medication had exacerbations and nearly 10% were deemed to have “treatment failure”.

These data cannot be used to advocate this rescue approach for

managing children with mild, persistent asthma, and I would be surprised if further research secures ethics approval on the basis of these data. As Martinez and colleagues state, the best treatment for these patients with mild persistent asthma is regular inhaled steroid, and that is what the current international asthma strategy states.⁵

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- 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**: 650–57.
- Checkley W. New insights into the treatment of persistent asthma. *Lancet* 2011; **377**: 614–16.
- Chapman KR, Barnes NC, Greening AP, Jones PW, Pedersen S. Single maintenance and reliever therapy (SMART) of asthma: a critical appraisal. *Thorax* 2010; **65**: 747–52.
- Demoly P, Louis R, Soes-Petersen U, et al. Budesonide/formoterol maintenance and reliever therapy versus conventional best practice. *Respir Med* 2009; **103**: 1623–32.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2010. <http://www.ginasthma.org/Guidelineitem.asp?i1=2&i2=1&intId=60> (accessed March 3, 2011).

Fernando Martinez and colleagues¹ report the use of rescue inhaled corticosteroids plus salbutamol in mild persistent asthma. We agree with them as regards the necessity of minimising treatment with inhaled corticosteroids, but we would like to focus on step-down therapy.

This strategy, according to guidelines,² often implies a slow tapering of



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inhaled corticosteroids once complete control is achieved for at least 3 months, lengthening the whole treatment period to several months. In our experience, treatment with inhaled corticosteroids for an average of 2 months (when asthma is poorly controlled) and then stopping abruptly, without any step-down therapy, is effective in preventing exacerbations in most cases. Application of this strategy in our area (Friuli Venezia Giulia, northeast Italy) has resulted in an inhaled corticosteroid consumption (number of beclomethasone dipropionate prescriptions per child per year) a third lower than that of other regions, without any increase in morbidity (number of salbutamol prescriptions per child per year).³

We underscore the need for less aggressive therapy in mild persistent asthma: in our experience the same goal can be achieved with a shortening of the control treatment course and the elimination of step-down therapy.

We declare that we have no conflicts of interest.

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- National Asthma Education and Prevention Program. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *Allergy Clin Immunol* 2007; **120** (suppl 5): S94–138.
- Berti I, Longo G, Visintini S. Treatment of mild asthma. *N Engl J Med* 2005; **353**: 424–27.

Authors' reply

We agree with Paul Brand that the evidence clearly indicates that daily inhaled corticosteroids are the most efficacious treatment for mild persistent asthma, and we stated this in several places in our paper. We also indicated, however, that there is ample evidence to suggest that adherence to such treatment is suboptimal and inconsistent, and a study has shown that it can drop to less than 60% of

prescribed days during long-term use in school-age children.¹ We also previously showed that a high proportion of children whose asthma was apparently uncontrolled by a combination of inhaled corticosteroids and long-acting β agonists were non-adherent to daily therapy even during a highly controlled run-in for a clinical trial.² This observation prompted us to find a therapeutic step-down approach for mild persistent asthma that would not require daily inhaled corticosteroid use, which is often an obstacle that many patients cannot overcome. We stress again that TREXA was not designed to determine whether rescue inhaled corticosteroid therapy can be used as first-line treatment in children who have not been shown to be responsive to daily inhaled corticosteroids.

We are less optimistic than Brand with respect to the long-term growth effects of long-term use of daily inhaled corticosteroids. Brand does not quote the recent follow-up of patients enrolled in the Childhood Asthma Management Program.³ The decreased mean height noted in the budesonide group relative to the placebo group at the end of that trial (1.1 cm; $p=0.005$) remained significant (0.9 cm; $p=0.01$) after an additional 4.8 years of follow-up. Therefore, to conclude that daily inhaled corticosteroids only “reset the growth clock temporarily” might be premature.

Mark Levy rightfully points out that, in TREXA, in children on rescue inhaled corticosteroid, 8.5% had treatment failure and 35% exacerbations, but rates for these outcomes in the two groups on daily inhaled corticosteroids were comparable: 2.8–5.6% and 28–31%, respectively. If anything, these results thus indicate that therapeutic approaches that are even more effective than inhaled corticosteroids in preventing asthma exacerbations are urgently needed.⁴

We agree with Elisa Panontin and Giorgio Longo that better step-down strategies for mild persistent asthma

are needed. We disagree, however, with the contention that stopping inhaled corticosteroids abruptly, without a plan to reintroduce them as needed or intermittently, is the better approach: the strategy proposed by Panontin and Longo was tested in our placebo group and resulted in an unacceptable proportion of treatment failures.

We declare that we have no conflicts of interest other than those stated in the original paper.

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- Nikander K, Turpeinen M, Pelkonen AS, Bengtsson T, Selroos O, Haahela T. True adherence with the Turbuhaler in young children with asthma. *Arch Dis Child* 2011; **96**: 168–73.
- Strunk RC, Bacharier LB, Phillips BR, et al. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. *J Allergy Clin Immunol* 2008; **122**: 1138–44.
- Strunk RC, Sternberg AL, Szeffler SJ, Zeiger RS, Bender B, Tonascia J. Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. *J Pediatr* 2009; **154**: 682–87.
- Martinez FD. Managing childhood asthma: challenge of preventing exacerbations. *Pediatrics* 2009; **123** (suppl 3): S146–50.

Health research— Europe's future

Meeting the newly-formed Biomed Alliance, the European Commission's Director of Health Research and Innovation, Ruxandra Draghia-Akli, said that “unless investment is maintained... on the entire path from academics to small and medium enterprises and industry, we risk falling behind” (Feb 12, p 541).¹ The European