



Asthma Treatment-2004

Jeffrey M Drazen

Editor-in-Chief, *New England Journal of Medicine*, Distinguished Parker B. Francis Professor of Medicine, Harvard Medical School.

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This review focuses on state of the art asthma treatment in 2004. It is based on the National Asthma Education and Prevention Program (NAEPP) panel Guidelines (Revision of 1997¹ and update of this revision for 2002²). This is a selective and interpretive review of the literature on this topic. Please note that my general comments are in this typeface; explanatory comments about published studies in this typeface and *my comments about the various studies are given in italic typeface.*

ASTHMA TREATMENT IS DICTATED BY ASTHMA SEVERITY

The type of treatment offered to an individual asthma patient is tailored to the severity of their disease. Patients with mild intermittent asthma³ comprise about half of all asthma patients. These patients do not require regular controller treatment but are appropriately managed using inhaled on an as needed basis only. Although there had been concerns about the regularly scheduled use of inhaled beta agonists^{4,5} these concerns have been resolved⁶. Patients who have infrequent asthma symptoms, are not troubled by nighttime awakenings from asthma, have near-normal airway function, and who are able to manage their symptoms of airway obstruction with the use of 30 puffs of albuterol a week or less⁷ do not require controller, i.e. regularly scheduled treatment.¹

In contrast patients with asthma symptoms more than twice a week, with more than three nocturnal awakenings per month and with impaired lung function (without bronchodilator treatment) require controller treatment. These patients are considered to have persistent asthma. There are three main categories of such individuals-those achieving asthma control with a single medication, those requiring two simultaneous asthma medications and those requiring more than two controller medications. Although the exact definition is more complex, the NAEPP terms these groups-mild, moderate and severe persistent asthma. The idea is that when asthma is controlled with medication, patients with persistent asthma have symptoms similar to those with intermittent asthma.

Although there are lots of complicated ways of looking at the problem-the simplest way is to ask-what is the least number of asthma medications that will control a patient's symptoms. Simply viewed patients with MILD INTERMITTANT ASTHMA will require a single asthma medication to control their condition.

MILD INTERMITTANT ASTHMA

Most patients fit in this category. For these patients, asthma is a nuisance not a major limiting factor in their lives. They do not require regular treatment with a controller medication; rather adequate treatment is achieved with the "as needed" use of an inhaled selective β_2 -adrenergic agonist, such as albuterol. Although there have not been randomized controlled trials, patients should be instructed to use their inhaled β_2 -adrenergic agonist about 15 minutes before engaging in exercise, or any other stimulus known to incite asthma. These treatments provide about 4-6 hours of bronchoprotection. Although they are very effective asthma treatments, there is clearly documented tachyphylaxis to their effects.⁸ If patients use these treatments on a more than daily basis, they lose their bronchoprotective effects.

In the first randomized prospective trial stratified by genotype in asthma, published in the *Lancet* in 2004⁹, the National Institutes of Health, Asthma Clinical Research Network showed that patients whose genomic DNA contained two copies of the beta₂-adrenergic with arginine encoded in the 16th position the regular use of inhaled albuterol was associated with an adverse effect on morning and afternoon peak flow, FEV₁, asthma symptoms and medication use. Patients with the adverse genotype did better when ipratropium bromide was used as an asthma treatment.

These data demonstrate that an individual's genotype at the beta₂-adrenergic receptor interacts with their response to asthma treatment with albuterol. In the United States, about one out six people has this adverse genotype. Although the prospective trial directing asthma care by genotype and showing an effect on asthma care has not been completed, it may make sense to think about using ipratropium bromide as a rescue bronchodilator in patients in whom albuterol use seems to lead to adverse asthma outcomes.

MILD PERSISTENT ASTHMA

What is the Natural History of Mild Persistent Asthma?

The Childhood Asthma Management Program¹⁰ examined 1041 children who were ages 5 to 12 at enrollment and assigned them, after run-in, to treatment with either inhaled budesonide (n=311, 400 μ g/day) or inhaled nedocromil (16 mg/day) for 4 to 6 years. There were 418 children assigned to placebo treatment for a similar period of time. The patients assigned to budesonide treatment had significantly fewer asthma exacerbations (prednisone courses, urgent care or hospitalizations for asthma)

than the placebo or the nedocromil groups, but there was no difference in the FEV₁ after bronchodilator treatment among the groups over the entire duration of the study. There was an effect of steroids on growth velocity, but only in the first year of the study. Four months after stopping treatment, the groups were similar in all measured respects.

This is a very important study with a large number of children studied for a long enough period of time to influence clinical practice. The data clearly show that steroids prevent asthma exacerbations-and hence are beneficial treatment. However, to me, the most important finding was that steroids had no long term effect on asthma progression. Thus although they are anti-inflammatory, their effects are not disease modifying. Simply put, inhaled steroids are simply symptomatic treatments-they have an effect while they are used, but no beneficial effects on disease progression. Based on the results of the CAMP study, we need to totally rethink the benefit of the anti-inflammatory effects of inhaled steroids in asthma.

The "START" study, published in 2003 in the *Lancet*¹¹ examined the utility of prescribing inhaled steroids to newly diagnosed mild asthmatics. The study compared patients receiving usual care, which did not include regular use of inhaled corticosteroids, with or without inhaled budesonide. There were over 7000 patients enrolled and followed for 3 years. There were 198 severe exacerbations in the placebo treatment group and 117 in the budesonide treatment group, the hazard ratio for a severe exacerbation was 0.56 (95% confidence interval 0.45 to 0.71, P<0.001). The group treated with budesonide had a slightly, but significantly, greater FEV₁ after bronchodilator (0.88%) after three years than the placebo group.

The sponsors of this study claim that the data strongly indicates the need for the treatment of newly diagnosed asthmatics with regular inhaled steroids. I disagree. A hundred patients need to be treated with inhaled steroids for a year to prevent an exacerbation, while all patients have side effects. Furthermore the children treated with inhaled steroids were 1 cm shorter than those not so treated; this difference in height can completely explain the difference in lung function, so the improvement in FEV₁ is largely artefactual. In my opinion inhaled steroids should not be used in patients with mild-intermittent asthma.

What is the best first-line treatment to use when patients are using monotherapy?

The answer to this question is only simple, *if you consider the data set from the perspective of a physician investigator and not from the patient's perspective.* The overwhelming majority of data in the literature support the idea that inhaled steroids are the most effective first-line monotherapy for asthma. Data from significant studies re-enforce this point of view.

Suissa and co-workers¹² used a nested case-control design to examine 30,569 patents from Saskatchewan, ages 5 through 44 years of age, who used anti-asthmatic drugs in the period from 1975 through 1991. Subjects were followed until they reached age 55, left the region, or died. There were 562 deaths in the cohort of which 77 were coded as due to asthma. They matched the 66 subjects for whom they had complete data with 2681 controls and calculated the rate ratio for death from asthma in cases and controls. They showed that the ratio decreased monotonically

Table 1: Inhaled Steroids in the US marketplace

Low Potency

Beclomethasone
Flunisolide
Triamcinolone

High Potency

Budesonide
Fluticasone
Mometasone (soon to be released)

with the amount of inhaled steroids used; the rate of death decreased by 21 percent with each canister of inhaled steroids used in the year prior to death.

This study was completed before the introduction of any controller therapies other than inhaled steroids, nedocromil sodium and disodium cromoglycate. This study adds to the data indicating that it makes sense to treat chronic persistent asthma with a controller medication, and demonstrates the effectiveness of inhaled steroids. It does not provide a basis for comparison among inhaled steroids.

Bleecker and colleagues¹³ studied 451 patients with mild-moderate persistent asthma (by symptoms) and compared asthma control, using lung function and asthma symptoms in patients treated with zafirlukast (Accolate®) 20 mg bid given orally or fluticasone dipropionate (Flovent®) 88 µg bid for 12 weeks. In this randomized blinded trial, fluticasone was superior to zafirlukast in all outcome indicators.

This trial is one of many that show a greater benefit of inhaled steroids, compared to anti-leukotrienes in the treatment of asthma¹⁴⁻¹⁸. These studies have all been of medium duration (6-18 weeks), thus the greater tendency for patients to stop treatment with inhaled medications compared to oral medications had little effect on outcome.

If one is to prescribe an inhaled corticosteroid, which is the "drug of choice"?

An immense amount of money has been spent by the makers of inhaled steroids to prove the superiority of their products and there is no clear winner. In my opinion there are two types of inhaled steroids on the market today-low potency and high potency steroids (Table 1). The low potency steroids have been around for three decades, are reasonably safe, are effective and very reasonably priced.

In a study supported by the National Institute of Health¹⁹ the beneficial (as defined by an improvement in FEV₁) and adverse (as defined by the decrease in the area under the morning plasma cortisol curve) effects of inhaled beclomethasone and inhaled fluticasone were compared. At the lowest dose given, two puffs a day, neither beclomethasone nor fluticasone had adverse effects on plasma cortisol and both improved the FEV₁ by about 10%. However, increasing the dose of inhaled fluticasone to 16 puffs a day resulted in increased suppression of the area under the cortisol curve (to about a 55% suppression) without beneficial effect on the FEV₁. In contrast, increasing the dose of beclomethasone to 32 puffs a day resulted in an additional 5% improvement in FEV₁ with less than a 20% suppression of the cortisol curve.

This study shows the power of pharmaceutical marketing. Fluticasone has been championed by its maker as a better inhaled

steroid, but for more money one gets less efficacy and more toxicity!

Are there adverse effects of inhaled corticosteroids?

Although the pharmaceutical industry would prefer that we believe otherwise, it stands to reason that are systemic effects of inhaled corticosteroids. However, these drugs are clearly effective asthma treatments. If we had treatments that were equally, or more effective than inhaled steroids, without any adverse effects, then we would use them as our first line therapy. The reality is that although inhaled steroids are very effective treatments, they have side effects-thus what are these effects and are they tolerable?

There will likely never be a simple answer to this question-so we must settle for more complex answers.

Is there an effect of inhaled steroids on height in children? The CAMP trial (reviewed above)¹⁰ measured a number of outcome indicators of the adverse effects of inhaled steroids. They found an effect of budesonide, at 400 µg/day, on growth velocity in the first year, but no effects on growth velocity or final height. They examined for subcapsular cataracts and found no effect of treatment on this outcome either, but they added the measurement after the trial was started so baseline examinations were not available for comparison in all the enrollees.

Agertoft and Pedersen²⁰ presented results of a long term prospective study of inhaled corticosteroids among children with asthma on the final obtained adult height of these children. They reported the results from 142 children treated with budesonide (mean daily dose was 412 µg/day-range 110 to 877). They used 18 asthmatic patients who had never received inhaled corticosteroids and 51 healthy siblings of asthmatic children as their control group. They observed, as did the CAMP investigators, that the onset of budesonide treatment was associated with a slowing of growth velocity, but the final height achieved was not altered by budesonide treatment.

Israel and co-workers²¹ examined the effects of inhaled steroid use on bone density in pre-menopausal women with asthma. They discarded women who had used oral steroids in any significant amount in the past. In a study with 3 years of follow-up they found that there was accelerated loss of bone in the hip and trochanter but not in the spine and femoral neck. The rate of bone loss was such “a woman with asthma who was treated with 1200 µg/day of inhaled corticosteroids beginning at age 30 and continuing through menopause at age 50 would have a predicted bone mass at the trochanter of 0.106 gm/cm² less than an untreated woman”. This would double the risk of hip fracture.

The overall outcomes of these three studies, the CAMP, the Agertoft and the Israel study, is that the low doses of inhaled steroids used are effective asthma control agents, the control comes at a cost, albeit minimal. At this time physicians should prescribe inhaled steroids for patients with asthma with the understanding that as patients with more mild disease are treated, that side effects must not be forgotten. Inhaled steroids are good symptomatic asthma treatments; I reserve their use for patients whose disease meets the definition of mild-to-moderate persistent asthma.

MODERATE AND SEVERE PERSISTENT ASTHMA

In my functional definition of moderate or severe persistent asthma, patients with moderate disease require treatment with two agents (in addition to rescue bronchodilator treatments) on a continuous basis. Thus it is reasonable to ask what are the best two way combinations for moderate persistent asthma

INHALED STEROIDS AND BETA-AGONISTS

The TRUST (The Regular Use of Salbutamol Trial) was a major study conducted in the United Kingdom and sponsored by the Medical Research Council. The trial was designed to determine if their was an adverse effect of regularly scheduled of inhaled beta agonists in patients with mild-moderate persistent asthma. Although this question had been largely resolved in patients with mild intermittent asthma through the BAGS trial⁶ there were no good data on the potential adverse effects of the regularly scheduled use of these agents in patients with more severe disease, especially those using inhaled corticosteroids. Indeed, the entire controversy arose because of findings of adverse effects with the regularly scheduled use of fenoterol in New Zealand.^{4,5} The TRUST investigators used a parallel group design to study the effects of regularly scheduled use of salbutamol (known in the US as albuterol) on asthma control. The studied 983 patients with moderate asthma, 90% of whom were using regularly scheduled inhaled corticosteroids; 497 patients were treated with regularly scheduled salbutamol delivered by a disk-haler, while 486 patients were treated with regularly scheduled placebo. Both groups of patients continued their usual daily treatment with open label inhaled corticosteroids. There were no differences in the “rate, timing or duration of exacerbations between the two groups”.

The BAGS and TRUST trials lay the issue to rest. The regularly scheduled use of inhaled salbutamol/albuterol has no adverse effects. However, in the absence of additional benefit, there is little reason to recommend the regularly scheduled treatment either. None of these studies considered genotype at the beta₂-adrenergic receptor as a factor in examining responses. As noted above, there is reason to believe that genotype at this receptor modifies the long term response to asthma treatment with beta₂ adrenergic agonists. Since only 1/6 patients harbors this genotype and since the genotype directed effect is modest, it is likely that a small adverse effect was missed in these studies

Inhaled steroids and long acting beta-agonists are good combination treatment.

The United States National Institute of Health sponsored Asthma Clinical Research Network published two studies on combination therapy. In the first²² patients whose asthma was well controlled on a low dose were switched to either inhaled salmeterol or continued on low dose inhaled steroids. The time to the first asthma exacerbation was significantly shorter in the group switched off inhaled steroids. In the second study²³ patients whose disease was only marginally controlled by low dose inhaled steroids had inhaled salmeterol added to their regimen. Later on the steroids were reduced or withdrawn in one group and maintained in the other. Inhaled steroid doses could be reduced with concomitant long acting beta agonist treatment but not stopped.

These two studies illustrate the major use, in my opinion, of inhaled beta agonists. We know that inhaled steroids have side effects. Since the dose of inhaled steroids can be reduced with the concomitant use of inhaled long acting beta agonists, it makes sense to use the combination, even though there have been no studies of long term side effects comparing higher doses of inhaled steroids versus lower doses of inhaled steroids plus long acting beta agonists in which side effects were an outcome indicator.

A number of companies have already introduced fixed dose combinations of inhaled steroids and long acting beta agonists for the treatment of moderate-to-severe persistent asthma. These dose combinations are based on the initial finding of Greening et al²⁴ that adding a long acting beta-agonist to the treatment regimen of a patient already receiving treatment with inhaled steroids was more effective than doubling the dose of inhaled steroids. These agents have been heavily promoted in Europe and it is anticipated that their sponsors will promote them heavily in the United States in the coming year.

Fluticasone (100µg) and salmeterol (50 µg) have been combined (SFC) in a single inhaler by Glaxo-Wellcome (Advair®). In a study published in June in the *Journal of Allergy and Clinical Immunology*²⁵ they compared the effects of treatment with a single entity in the combination with the results of combination therapy. To be eligible for the study patients had to have an FEV₁ between 40 and 85 percent of predicted and a bronchodilator response to inhaled albuterol. Eligible patients then had their drugs stopped for two weeks, except for their rescue albuterol, and then were allocated to receive one or both of the randomized treatments. There was a significantly greater effect of the combined treatment compared to placebo, or the individual components of the therapy.

This fixed dose combination product is being hailed by its maker as a major advance in asthma treatment, but in my opinion, it is a giant step sideways! The trial discussed above, and many of the others conducted by Glaxo, have used this study design where the inclusion criteria selectively identify patients who benefit from either of the components of the combination treatment, thus the very hard to treat patients are excluded from the study. Most worrisome however is the use of fixed dose combinations with a high dose (100 µg or higher) of fluticasone. If the purpose of the combination is to prevent the adverse effects of inhaled corticosteroids, the use of lower doses of inhaled steroids is mandatory.

The combination of inhaled long acting beta-agonist and inhaled steroids is an effective one and useful in asthma treatment. The use of fixed dose-combination therapy is a major mistake as it prevents the easy down-titration of the steroid dose. This should be the goal of asthma treatment, but until the manufacturer provides combinations with very low doses of inhaled steroids, the enhanced compliance gained by having the combination product will be offset by long term adverse effects.

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