

Considering therapeutic options in the real world

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When choosing a drug regimen, physicians can rely on two models: their own clinical experience and results from clinical trials. Both options have problems. Overall, patients with persistent asthma symptoms often have improved outcomes with the use of long-term controller medications on a daily basis to prevent exacerbations of symptoms. Inhaled corticosteroids (ICSs) are generally recognized as being the most effective treatment for the underlying inflammatory characteristics of asthma. However, despite adequate dosing, some patients with persistent asthma remain symptomatic while taking an ICS. Therefore, it may be beneficial to administer combination therapy with an ICS and a long-acting β -agonist (LABA) in this subset of asthma patients. Another anti-inflammatory choice for persistent asthma is the leukotriene receptor antagonist (LTRA), either as monotherapy or in combination with an ICS. Regardless of what treatment regimen a physician chooses to prescribe, the choice of medication depends on many factors, including patient preference, physician comfort with the regimen, and cost. (*J Allergy Clin Immunol* 2003;112:S112-5.)

Key words: Asthma, inhaled corticosteroids, long-acting β -agonists, leukotriene receptor antagonists

Current asthma treatment guidelines suggest that patients use long-term controller medications on a daily basis to achieve and maintain control of persistent asthma symptoms. Although inhaled corticosteroids (ICSs) are commonly used, other treatment options include long-acting β -agonists (LABAs) and leukotriene receptor antagonists (LTRAs). ICSs and LTRAs can be used alone or in combination with each other or with LABAs. In the clinical setting, treatment choice is dependent on disease severity and frequency, age of the patient, and in some cases, patient and physician preference.

When choosing a drug regimen, physicians can rely on two models: their own clinical experience and results from clinical trials. Both options have problems. Decisions based on personal experience are prone to personal bias; chances are, most physicians only remember good outcomes. Also, because personal experience is limited to the size of an individual practice, the sample of patients the experience is based on is very small. Results from clinical trials can also be biased. Adherence to medication

Abbreviations used

BDP: Beclomethasone dipropionate
DPI: Dry powder inhaler
FEV₁: Forced expiratory volume at one second
FP: Fluticasone propionate
ICS: Inhaled corticosteroid
LABA: Long-acting β -agonist
LTRA: Leukotriene receptor antagonist
MDI: Metered dose inhaler

is generally better during a trial than in clinical practice. Also, studies sponsored by for-profit companies tend to significantly favor the experimental drug; the same bias is not seen in studies sponsored by nonprofit organizations.¹ However, despite these issues, treatment is only advanced by double-blind, placebo-controlled, randomized studies. Therefore, whereas personal experience plays a role in treatment decision-making, results obtained from large, balanced trials must also be considered.

INHALED CORTICOSTEROIDS

Inhaled corticosteroids are currently the first-line treatment of choice for prevention of persistent asthma.^{2,3} They are generally recognized as being the most effective treatment for the underlying inflammatory characteristics of asthma.³ In clinical trials, ICSs have been shown to significantly decrease airway hyperresponsiveness, effectively prevent acute exacerbations, improve lung function, and reduce symptom severity.² Some evidence does exist, though, that higher doses and prolonged use of ICSs can elicit systemic side effects.⁴

There are many different ICS preparations and delivery methods available for asthma treatment. Although numerous safety and efficacy studies have been conducted, no standardized method to compare beneficial and adverse effects of these drugs has been developed. To this end, Szeffler et al⁴ conducted a parallel, open-label, multicenter study to compare the relative beneficial and systemic effects in a dose-response relationship for two ICSs. Beclomethasone dipropionate (BDP) and fluticasone propionate (FP) were both administered by use of a pressurized, metered dose inhaler (MDI).⁴ An evaluation of systemic effects with multiple measures of beneficial effects was combined to introduce a benefit-to-risk comparison model for this class of drug.⁴

A total of 30 asthmatic subjects, aged 18 to 55 years, were randomized to receive either BDP MDI or FP MDI in increasing doses for 3 consecutive 6-week intervals

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0091-6749/2003 \$30.00 + 0
doi:10.1067/mai.2003.1857

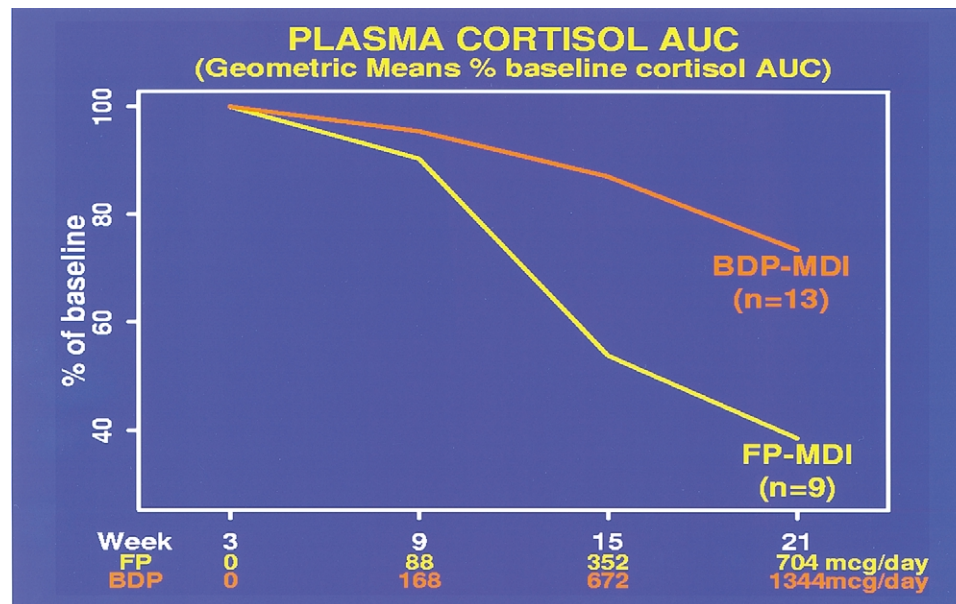


FIG 1. A total of 30 asthmatic subjects, aged 18 to 55 years, were randomized to receive either BDP MDI or FP MDI in increasing doses for 3 consecutive 6-week intervals (low, medium, and high dose). All subjects then received an additional 3 weeks of high-dose (2000 µg/d) FP DPI. Overnight plasma cortisol suppression increased in a dose-depressed manner for both BDP MDI and FP MDI. The results of this study demonstrate that low-to-medium doses of ICSs are needed to attain near maximal increases in FEV₁ and methacholine PC₂₀. When drug doses were increased to beyond what was needed for near maximal results, a resulting suppression of overnight cortisol levels occurred in a dose-dependent manner. Subsequently, the therapeutic index of both drugs diminished as the dose increased. (Adapted with permission from Szefer et al. *J Allergy Clin Immunol* 2002;109:410-8.)

(low, medium, and high dose).⁴ All subjects then received an additional 3 weeks of high-dose (2000 µg/d) FP dry powder inhaler (DPI). “Benefit” was assessed by improvements in forced expiratory volume at one second (FEV₁) and PC₂₀.⁴ “Risk” was assessed by overnight plasma cortisol suppression.⁴ Maximum FEV₁ response was seen with the low dose of FP MDI and the medium dose of BDP MDI.⁴ Similarly, near-maximum methacholine PC₂₀ improvements occurred with the low dose of FP MDI and the medium dose of BDP MDI.⁴ There was a high degree of variability in response to ICSs for two important efficacy measures, FEV₁ and methacholine PC₂₀. Approximately one third of study subjects demonstrated a poor response to each measure.⁴ Overnight plasma cortisol suppression increased in a dose-depressed manner for both BDP MDI and FP MDI (Fig 1).⁴

There was a difference in dose-response profiles for efficacy and systemic effects with both drugs. The maximum lung function benefits were achieved at a medium dose of BDP MDI, with little effect on cortisol levels.⁴ Bronchial reactivity was further improved with the high dose of BDP MDI; however, this higher dose resulted in a 20% increase in overnight cortisol suppression.⁴ Similarly, low doses of FP MDI resulted in maximum improvements in lung function. Medium doses of FP MDI led to further improvement in airway hyperresponsiveness, but significantly increased overnight cortisol suppression.⁴

The results of this study demonstrate that low-to-medium doses of ICSs are needed to attain near maximal increases in FEV₁ and methacholine PC₂₀.⁴ When drug doses were increased to beyond what was needed for near maximal results, a resulting suppression of overnight cortisol levels occurred in a dose-dependent manner. Subsequently, the therapeutic index of both drugs diminished as the dose increased.⁴

This study design may be useful as a model for future studies seeking to determine the risk-to-benefit ratio of comparable ICSs. However, because of the significant variability in response, an effective study would need to include a large number of subjects to define an efficacy dose-response relationship.⁴

COMBINATION THERAPY WITH INHALED CORTICOSTEROIDS AND LONG-ACTING β-AGONISTS

Despite adequate dosing, some patients with persistent asthma remain symptomatic while taking an ICS. Results from clinical studies suggest that it may be beneficial to administer combination therapy with an ICS and a LABA in this subset of asthma patients.⁵⁻⁷ In one study, patients taking a lower-dose ICS with a LABA had better lung function and symptom control compared with patients receiving double the dose of the ICS alone.⁵ In a similar

study, patients on a high-dose ICS with poorly controlled asthma had improved lung function and symptom control when a LABA was added to their treatment regimen.⁶

An analysis of two double-blind, randomized clinical trials evaluated the rates and characteristics of asthma exacerbations in patients receiving a high-dose ICS alone compared with a low-dose ICS plus a LABA.⁸ A total of 925 patients 12 years of age and older who were already receiving 88 µg twice daily of FP were randomly assigned to receive either 88 µg of FP and 42 µg of salmeterol, or 220 µg FP twice daily for 24 weeks.⁸

The addition of salmeterol to FP therapy resulted in a significantly lower rate and number of asthma exacerbations compared with the higher dose FP. A total of 41 (8.8%) patients had 47 exacerbations with the addition of salmeterol compared with 63 (13.8%) patients with 75 exacerbations in the group receiving increased-dose FP ($P = .017$).⁸ Salmeterol plus low-dose FP was significantly more protective than increased-dose FP in preventing asthma exacerbations, as shown by the time to first exacerbation ($P < .05$).⁸ In both groups, clinical indicators of worsening asthma showed parallel changes before asthma exacerbation, and more rapid improvements were observed after treatment of the exacerbation with salmeterol compared with higher-dose FP.⁸

There has been some discussion regarding the mechanism by which LABAs and ICSs interact with resulting improved efficacy compared with either drug alone. LABAs work by stimulating β_2 -receptors, which results in increased cyclic adenosine monophosphate. This subsequently leads to reduced bronchoconstriction.² ICSs activate the glucocorticoid receptor, a transcription factor present in most cell types.⁹ Once activated, the glucocorticoid receptor produces pronounced anti-inflammatory effects, characterized by decreased expression of inflammatory mediators or increased expression of protective mediators.⁹ ICSs have also been shown to induce transcription of the β_2 -AR gene, an effect that improves the therapeutic efficacy of β_2 -AR agonists.⁹ Recent data has shown that β_2 -AR agonists are also capable of activating the glucocorticoid receptor.⁹ This seems to explain, at least in part, why combining an ICS with a LABA provides more effective anti-inflammatory protection compared with ICSs alone.

COMBINATION THERAPY WITH INHALED CORTICOSTEROIDS AND LEUKOTRIENE RECEPTOR ANTAGONIST

An addition to the anti-inflammatory choices for persistent asthma is the LTRA. These drugs work by inhibiting cysteinyl leukotriene molecules late in the inflammatory process. Whereas monotherapy with LTRAs has been inconsistent, with some studies showing only a modest improvement in lung function and asthma symptoms, the addition of an LTRA to ICS therapy has been promising.² In addition to efficacy, compliance may improve with LTRA combination therapy. Compliance with inhaled medications is generally less than that seen with oral med-

ications.¹⁰ Because LTRAs are oral medications, patients may be more likely to comply to a treatment regimen containing one oral and one inhaled medication compared with a regimen with two inhaled medications.¹⁰

Lavolette et al¹⁰ conducted a study to determine whether montelukast, an oral LTRA, would provide any additional benefit to the effects seen with standard ICSs. A total of 642 patients with chronic symptomatic asthma despite treatment with inhaled beclomethasone, 200 µg twice daily were randomly assigned to one of four treatment groups: montelukast 10 mg plus continuing inhaled beclomethasone; placebo tablet plus continuing inhaled beclomethasone; montelukast 10 mg and inhaled placebo (after blind beclomethasone removal); and placebo tablet and inhaled placebo (after blind beclomethasone removal). The primary endpoints were FEV₁ and daytime asthma symptoms score. Patients receiving montelukast and beclomethasone had improved FEV₁, daytime asthma symptom scores, and nocturnal awakenings compared with patients receiving beclomethasone alone ($P < .05$).¹⁰ The authors concluded that montelukast provided additional asthma control to patients benefiting from, but incompletely controlled on, inhaled beclomethasone.¹⁰

Whereas LTRAs improve asthma symptoms when added to ICS monotherapy, this combination may not be as effective as the combination of ICSs and LABAs. Nelson et al¹¹ compared the efficacy and safety of FP/salmeterol combination administered through a Diskus inhaler (Advair; GlaxoSmithKline, Research Triangle Park, NC) versus montelukast added to FP in patients whose symptoms were poorly controlled with ICS therapy. This double-blind, parallel-group, 12-week study included 447 patients with asthma who were symptomatic at baseline while receiving low-dose FP.¹¹ Patients were treated with one of the following: combination of FP 100 µg plus salmeterol 50 µg twice daily, or FP 100 µg twice daily plus oral montelukast 10 mg once daily.¹¹ The FP/salmeterol combination provided better overall asthma control than the FP/montelukast combination. Asthma exacerbation rates were significantly lower in the FP/salmeterol combination group compared with the FP/montelukast combination group.¹¹ The authors concluded that symptomatic patients on low-dose ICS therapy had significantly greater improvement in asthma control when they were switched to a combination containing a LABA compared with a combination containing an LTRA.¹¹

A randomized, placebo-controlled, double-blind study comparing the clinical benefits of montelukast and inhaled beclomethasone in 895 patients with chronic asthma found that over a 12-week period, the average percentage change from baseline in FEV₁ was 13.1% with beclomethasone, 7.4% with montelukast, and 0.7% with placebo ($P < .001$ for each compared with placebo; $P < .01$ for beclomethasone compared with montelukast).¹² The average change from baseline in daytime symptom score was -0.62 for beclomethasone, -0.41 for montelukast, and -0.17 for placebo ($P < .001$ for each treatment compared with placebo; $P < .01$ for beclomethasone compared with montelukast).¹² Both

montelukast and beclomethasone improved peak expiratory flow rates and quality of life, reduced nocturnal awakenings and asthma attacks, increased the number of asthma-control days, and decreased the number of days with asthma exacerbations.¹² The authors concluded that although beclomethasone had a greater mean clinical benefit than montelukast, montelukast had a faster onset of action and a greater initial effect.¹²

One theory for the inconsistent efficacy levels noted with LTRAs is that the patient population can be divided into responders and nonresponders, with an estimated 40% to 50% of patients classified as nonresponders. Therefore, overall response rate to LTRAs is decreased.¹² However, both beclomethasone and montelukast showed a similar distribution pattern of response, suggesting that the reason why some patients respond to LTRAs and some do not may be more complex than a simple “responders” versus “nonresponders” division. Rather, tracking response patterns within many different patient groups may help better define why some patients respond to LTRA therapy and some do not.¹²

CONCLUSIONS

There are many options for patients with persistent asthma. Although current preventive treatment regimens offer improved efficacy for patients with asthma compared with what was available several decades ago, there are still subsets of patients who respond poorly despite the medication. Additional clinical studies with existing medications, as well as the development of new and novel therapies, may help provide relief for these patients. However, to ensure effective treatments, future studies need to address the variability of response seen in many published studies. The risk/benefit ratio of any new drug, as well as many older drugs, needs to be clearly stated so that physicians and patients can make the choice that is best for their individual situation. Additional patterns of response distribution need to be studied in a wide variety of patient populations so that subgroups of patients who will not respond can be targeted. Ultimately, the choice of medication depends on many factors, including patient preference, physician comfort, and cost.

I thank Maria Bavishi for her assistance in preparing and editing this manuscript.

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