CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will consider prescribing inhaled corticosteroids to their patients who have mild persistent asthma

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should patients with mild asthma use inhaled steroids?

SUSAN RAZAVI ABOUHASSAN, MD
Respiratory Institute, Cleveland Clinic

DAVID M. LANG, MD*
Head, Allergy/Immunology Section, and Co-director, Asthma Center, Respiratory Institute, Cleveland Clinic

Studies show long-term, low-dose inhaled corticosteroids are favorable from a risk-benefit standpoint in mild persistent asthma

A: Yes. A number of large randomized controlled trials have shown inhaled corticosteroids to be beneficial in low doses for patients who have mild persistent asthma, and therefore these drugs are strongly recommended in this situation.[1]

Asthma care providers should, however, consider this "yes" in the context of asthma severity, the goals of therapy, and the benefits and risks associated with inhaled corticosteroids.

CLASSIFICATION OF ASTHMA SEVERITY

The third Expert Panel Report (EPR-3) categorizes asthma as intermittent (formerly called "mild intermittent"), mild persistent, moderate persistent, or severe persistent (TABLE 1).[1]

Although the studies of asthma prevalence had methodologic limitations and therefore the true prevalence of mild persistent asthma cannot be determined, it is common. Fuhlbrigge et al[2] reported that most asthma patients have some form of persistent asthma. In contrast, Dusser et al[3] reviewed available studies and concluded that most patients with asthma have either intermittent or mild persistent asthma.

GOALS: REDUCE IMPAIRMENT AND RISK

The goals of asthma management are to:

Reduce impairment by controlling symptoms so that normal activity levels can be maintained, by minimizing the need for short-acting bronchodilator use, and by maintaining normal pulmonary function; and to

Reduce risk by preventing progressive loss of lung function and recurrent exacerbations, and by optimizing pharmacotherapy while minimizing potential adverse effects.[1]

EVIDENCE OF BENEFIT

The benefits of inhaled corticosteroids in mild persistent asthma were established by a number of large prospective clinical trials (TABLE 2).[4–8]

The OPTIMA trial[4] (Low Dose Inhaled Budesonide and Formoterol in Mild Persistent Asthma) was a double-blind, randomized trial carried out in 198 centers in 17 countries. Compared with those randomized to receive placebo, patients who were randomized to receive an inhaled corticosteroid, ie, budesonide (Pulmicort) 100 µg twice daily, had 60% fewer severe exacerbations (relative risk [RR] 0.4, 95% confidence interval [CI] 0.27–0.59) and 48% fewer days when their asthma was poorly controlled (RR 0.52, 95% CI 0.4–0.67). Adding a long-acting beta-agonist did not change this outcome.

The START study[5] (Inhaled Steroid Treatment as Regular Therapy in Early Asthma) showed that, compared with placebo, starting inhaled budesonide within the first 2 years of asthma symptoms in patients with mild persistent asthma was associated with better asthma control and less need for additional asthma medication.

*Dr. Lang has disclosed receiving honoraria for teaching and speaking from Merck Schering-Plough, Genentech-Novartis, sanofi-aventis, GlaxoSmith-Kline, and AstraZeneca, and honoraria for consulting from GlaxoSmith Kline, AstraZeneca, and MedImmune.

doi:10.3949/ccjm.77a.09074

TABLE 1

Classification of asthma severity

	INTERMITTENT	MILD PERSISTENT	MODERATE PERSISTENT	SEVERE PERSISTENT
Measures of impairment				
Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
Nighttime awakenings	≤ 2 times/month	3–4 times/month	More than once a week, but not nightly	Often, seven times a week
Short-acting beta agonist use for symptom control	≤ 2 days/week	> 2 days/week but not daily, and not more than once on any day	Daily	Several times a day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	Normal FEV_1 between exacerbations	FEV_1 > 80% of predicted	FEV_1 > 60% but < 80% predicted	FEV_1 < 60% of predicted
	FEV_1 > 80% of predicted	FEV_1/FVC normal	FEV_1/FVC reduced by ≤ 5%	FEV_1/FVC reduced by >5%
	FEV_1/FVC normal			
Measures of risk				
Exacerbations requiring oral systemic corticosteroids	0–1/year	≥ 2/year	≥ 2/year	≥ 2/year

FEV_1 = forced expiratory volume in the first second of expiration; FVC = forced vital capacity

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The IMPACT study[6] (Improving Asthma Control Trial) showed that inhaled steroids need to be taken daily, on a regular schedule, rather than intermittently as needed. Patients received either inhaled budesonide as needed, budesonide 200 µg twice daily every day, or zafirlukast (Accolate) 20 mg twice daily. Daily budesonide therapy resulted in better asthma control, less bronchial hyperresponsiveness, and less airway inflammation compared with intermittent use, zafirlukast therapy, or placebo. Daily zafirlukast and intermittent steroid treatment produced similar results for all outcomes measured.

Despite this strong evidence supporting regular use of inhaled corticosteroids in patients with mild persistent asthma, many patients choose to take them intermittently.

Suissa et al[7] found, in a large observational cohort study, that fewer patients died of asthma if they were receiving low-dose inhaled corticosteroids than if they were not. The rate of death due to asthma was lower in patients who had used more inhaled corticosteroids over the previous year, and the death rate was higher in those who had discontinued inhaled corticosteroids in the previous 3 months than in those who continued using them.

STEROIDS DO NOT SLOW THE LOSS OF LUNG FUNCTION

Compared with people without asthma, asthma patients have substantially lower values of forced

TABLE 2

Inhaled corticosteroids for mild persistent asthma: Evidence of benefit

STUDY	RESULTS
OPTIMA[4]	60% fewer serious exacerbations with budesonide (Pulmicort) 100 µg twice daily vs placebo, number needed to treat = 5; no benefit of added formoterol (Foradil) 4.5 µg twice daily
	48% fewer poorly controlled days with budesonide vs placebo, number needed to treat = 14.5; no benefit of added formoterol
	Formoterol increased lung function; no change in other end points
START[5]	Significantly lower risk of a severe asthma-related event with budesonide 400 µg (200 µg for those under age 11 years) vs placebo (odds ratio 0.61, $P < .001$)
IMPACT[6]	Compared with intermittent budesonide or continued zafirlukast (Accolate) use, continuous budesonide use (200 µg twice daily) resulted in greatest improvement in prebronchodilator FEV_1 ($P < .005$), bronchial reactivity ($P < .001$), sputum eosinophils ($P < .006$), exhaled nitric oxide ($P < .007$), and symptom-free days ($P < .03$)
	Zafirlukast 20 mg twice daily was similar to intermittent budesonide for all outcomes measured
Suissa et al[7]	21% lower rate of death for each canister of inhaled corticosteroid used in the previous year
	Rate of death in first 3 months after discontinuation of inhaled corticosteroids was higher than in those who continued inhaled steroids
Busse et al[8]	Significantly greater improvement in symptom scores, percentage of symptom-free and albuterol-free days, albuterol use, and nighttime awakenings in patients on fluticasone (Flovent) 88 µg twice daily vs those on zafirlukast 20 mg twice daily ($P < .05$) or placebo ($P < .05$)
	4% of fluticasone patients required oral corticosteroids for exacerbation vs 12% in zafirlukast group and 10% in placebo group

OPTIMA = Low Dose Inhaled Budesonide and Formoterol in Mild Persistent Asthma; START = Inhaled Steroid Treatment as Regular Therapy in Early Asthma; IMPACT = Improving Asthma Control Trial

expiratory volume in the first second of expiration (FEV_1). They also have a faster rate of functional decline: the average decrease in FEV_1 in asthma patients is 38 mL per year, compared with 22 mL per year in nonasthmatic people.[9]

Although inhaled corticosteroids have been shown to increase lung function in asthma patients in the short term, there is little convincing evidence to suggest that they affect the rate of decline in the long term.[10] In fact, airway inflammation and bronchial hyperresponsiveness return to baseline within 2 weeks after inhaled corticosteroids are discontinued.[10]

DO INHALED CORTICOSTEROIDS STUNT CHILDREN'S GROWTH?

The safety of long-term low-dose inhaled corticosteroids is well established in adults. However, two large randomized controlled trials found that children treated with low-dose inhaled steroids (budesonide 200–400 µg per day) grew 1 to 1.5 cm less over 3 to 5 years of treatment than children receiving placebo.[11] However, this effect was primarily evident within the first year of therapy, and growth velocity was similar to that with placebo at the end of the treatment period (4 to 6 years).[12]

Agertoft and Pedersen[13] found that taking inhaled corticosteroids long-term is unlikely to have an effect on final height. Children who took inhaled budesonide (up to an average daily dose of 500 µg) into adulthood ended up no shorter than those who did not.

Based on these and other data, inhaled corticosteroids are generally considered safe at recommended doses. However, the decision to prescribe them for long-term therapy should be based on the risks and benefits to the individual patient.[1]

TABLE 3

Estimated comparative daily dosages of inhaled corticosteroids in patients age 12 and older

DRUG	LOW DAILY DOSE	MEDIUM DAILY DOSE	HIGH DAILY DOSE
Beclomethasone HFA (QVAR) 40 or 80 µg/puff	80–240 µg	> 240–480 µg	> 480 µg
Budesonide DPI (Pulmicort) 90, 180, or 200 µg/inhalation	180–600 µg	> 600–1,200 µg	> 1,200 µg
Flunisolide (AeroBid) 250 µg/puff	500–1,000 µg	> 1,000–2,000 µg	> 2,000 µg
Flunisolide HFA (Aerospan) 80 µg/puff	320 µg	> 320–640 µg	> 640 µg
Fluticasone (Flovent)			
HFA/MDI: 44, 110, or 220 µg/puff	88–264 µg	> 264–440 µg	> 440 µg
DPI: 50, 100, or 250 µg/inhalation	100–300 µg	> 300–500 µg	> 500 µg
Mometasone DPI (Asmanex) 200 µg/inhalation	200 µg	400 µg	> 400 µg
Triamcinolone acetonide (Azmacort) 75 µg/puff	300–750 µg	> 750–1,500 µg	> 1,500 µg

DPI = dry-powder inhaler; HFA = hydrofluoroalkane; MDI = metered-dose inhaler

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Outcomes are better with daily than with as-needed inhaled corticosteroid therapy

ALTERNATIVE DRUGS FOR MILD PERSISTENT ASTHMA

Leukotriene-modifying drugs include the leukotriene receptor antagonists montelukast (Singulair) and zafirlukast and the 5-lipoxygenase inhibitor zileuton (Zyflo CR). These drugs have been associated with statistically significant improvement in FEV_1 compared with placebo in patients with mild to moderate asthma, reductions in both blood and sputum eosinophils,[14] and attenuation of bronchoconstriction with exercise.[11]

Large randomized trials comparing leukotriene modifier therapy with low-dose inhaled steroids in adults and children with mild persistent asthma have found that although outcomes improve with either therapy, the improvement is statistically superior with inhaled steroids for most asthma-control measures.[6,8] Low-dose inhaled steroid therapy in patients with mild persistent and moderate persistent asthma has been associated with superior clinical outcomes as well as greater improvement in pulmonary function than treatment with antileukotriene drugs (**TABLE 2**).[8]

Asthma is heterogeneous, and properly selected patients with mild persistent asthma may achieve good control with leukotriene-modifier monotherapy.[15] Alternatives for patients with mild persistent asthma include the methylxanthine theophylline, but this drug is less desirable due to its narrow therapeutic index.[1] The inhaled cromones nedocromil (Tilade) and cromolyn (Intal) were other options in this patient population, but their short half-lives made them less practical, and US production has been discontinued.

THE BOTTOM LINE

Inhaled corticosteroids are the most effective drug class for controlling mild persistent asthma and are generally regarded as safe for long-term

use in children and adults. TABLE 3 lists the estimated comparative daily dosing of inhaled corticosteroids for patients over 12 years of age. The EPR3 guidelines[1] include comparative daily dosages for patients younger than age 12.

Though leukotriene receptor antagonists can be effective, the daily use of inhaled corticosteroids results in higher asthma control test scores, more symptom-free days, greater pre-bronchodilator FEV_1, and decreased percentage of sputum eosinophils[6] in patients with mild persistent asthma, and the addition of a long-acting beta agonist does not provide additional benefit.[4] Furthermore, daily use of inhaled corticosteroids in these patients has also been associated with a lower rate of asthma-related deaths and with less need for systemic corticosteroid therapy,[7,8] even though inhaled corticosteroids have not yet been shown to alter the progressive loss of lung function.[10]

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***ADDRESS**: Susan Razavi Abouhassan, MD, Respiratory Institute, A90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail abouhas@ccf.org.*