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As-needed inhaled corticosteroids for mild persistent asthma

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As-Needed Inhaled Corticosteroids for Mild Persistent Asthma

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Background

Mild persistent asthma is one of four severity level classifications used by the National Asthma Education and Prevention Practice (NAEPP) Guideline for the Diagnosis and Management of Asthma.[1] It is classified on the basis of clinical symptoms before treatment. Mild persistent asthma is categorized on the basis of symptoms occurring on greater than two days per week but less than once daily or greater than two nights per month as well as spirometry measures of forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) $\geq$ 80% and PEF variability of < 20%.[2]

Recommended long-term control treatment for mild persistent asthma is daily low-dose inhaled corticosteroids. Guideline-suggested alternative treatments include daily cromolyn, leukotriene modifiers, nedocromil, or sustained release theophylline with serum levels maintained between five to 15 mcg/mL. Quick relief therapy with a short-acting, inhaled beta-2 bronchodilator is recommended as needed.[2]

Because of the variability in frequency and intensity of mild persistent asthma symptoms, patients may not adhere to daily use of inhaled corticosteroids but rather use them intermittently.[3,4]

Citation

Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. N *Engl J Med* 2005;352:1519-28.

Methods

In this multicenter, double-blind trial, 225 adult patients (18 to 65 years of age) with physician-diagnosed asthma who met evidence-based mild persistent asthma criteria were randomized to one of three treatment groups. Seventy-three patients received inhaled budesonide 200 mcg twice daily plus zafirlukast placebo tablets twice daily. Seventy-six patients received zafirlukast 20 mg tablets twice daily plus a placebo inhaler (*Turbuhaler*) one puff twice daily. The third group of 76 patients received placebo zafirlukast tablets twice daily and a placebo inhalation of one puff twice daily.

All three treatment groups received either "open-label" inhaled budesonide 800 mcg twice daily for ten days or oral prednisone (0.5mg/kg) daily for five days if their asthma exacerbated.

Both the initial treatment phase prior to randomization (run-in phase) and the after-study treatment phase consisted of a ten to 14 day period of therapy with oral prednisone (0.5 mg/kg/day), 800 mcg inhaled budesonide twice daily, and zafirlukast 20 mg twice daily, plus as-needed inhaled albuterol (540 to 720 mcg) to eliminate any causes of airway flow obstruction.

Participants were followed for one year. Routine visits were conducted and study parameters were recorded. FEV_1 treatment adherence, asthma control (using a questionnaire), medication side effects, and symptom-related difficulties and days were measured, assessed, and discussed. Daily diaries were kept by participants during certain periods of the study. Peak flow and other personal observations were recorded by the subjects.

Results

One hundred ninety-nine patients completed the study. Patients followed the prescribed treatment regimens greater than 90% of the time. This level of adherence to protocol was similar in all groups.

The change in morning PEF, the primary study outcome, was similar in all treatment groups. The morning PEF value increases were 8.3% in the daily budesonide group, 7.9% in the daily zafirlukast group, and 7.1% in the intermittent treatment group (P = 0.90) corresponding to an

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approximate 7.8% increase (32 liters per minute). Kaplan-Meier estimates of the time to a first exacerbation of asthma were similar for all treatment groups (P=0.39). Similarly, there was no difference in multiple event exacerbations per patient in all treatment groups (P=0.24). Compared with the daily zafirlukast and intermittent therapy groups, the daily budesonide group showed the greatest improvements in the secondary outcomes of pre-bronchodilator FEV_1 (P=0.005), asthma control score (P<0.001), and number of symptom-free days score (P=0.03). The treatment groups did not differ in the secondary outcome parameters of post-bronchodilator FEV_1 scores (P=0.29) or asthma quality of life scores (P=0.18).

Author Conclusions

The authors concluded that it is possible to treat chronic mild persistent asthma in adults with short, intermittent courses of inhaled or oral corticosteroids whenever asthma exacerbations occur. They caution that longer and larger studies will be needed before this treatment approach can be recommended.

Commentary

As the authors suggest, this novel approach to treating mild persistent asthma in adults will require further validation before it can be accepted as a treatment option. The reality of patient adherence to daily inhaled corticosteroid use for mild persistent asthma is doubtful. Patients with mild persistent asthma may not experience exacerbations on a daily basis or their symptoms are so mild that they "forget" or do not use their prescribed treatment. Some may be concerned about the safety of using long-term inhaled steroids or the cost of medication. Yet, as demonstrated in this study, it is possible to treat patients with mild persistent asthma with intermittent inhaled or oral corticosteroids [Evidence level A; high-quality RCT].[3]

This study was the first trial conducted by the Asthma Clinical Research Network (ACRN) which was established in 1993 by the Division of Lung Diseases (DLD), and the National Heart, Lung and Blood Institute (NHLBI). This study by Boushen et al is entitled: **IMP**roving **A**sthma **C**ontrol **T**rial (IMPACT).[3,5]

One of the questions concerning this trial focuses on the cost associated with the daily use of "controller" therapy in asthma. Using the ACRN mild persistent asthma prevalence and cost assumptions, daily inhaled corticosteroid use for mild persistent asthma treatment would increase expenditures by over two billion dollars each year. Results from IMPACT may assist in answering this question.[6] The National Asthma Education and Prevention Program (NAEPP) will use the results from IMPACT to update guidelines in 2006.

In IMPACT, 411 patients initially met the criteria for mild persistent asthma, yet on further screening, 64 patients were identified with higher severity asthma and 30 patients had milder forms of asthma. As Boushey et al discuss in their trial publication, the lack of a difference in the treatment groups may reflect the low rate of asthma exacerbation.[3] Only adults who were nonsmokers with a long history of asthma and a lower incidence of exacerbation were included. The low percentage of eosinophils in sputum (median range 0.4% to 0.6%) and the low nitric oxide concentration in patient exhalations (median range 16.4 to 16.8 parts per billion) may suggest that the study population had a very mild form of persistent asthma.[7]

Does as-needed use of inhaled corticosteroids predispose mild persistent asthma patients to more severe asthma and the progressive loss of lung function? This question remains unanswered. No randomized clinical studies have addressed asthma outcomes when airway inflammation is not suppressed on a daily basis.[7]

A recommendation for the use of as-needed inhaled corticosteroids for patients with mild persistent asthma must be considered carefully. This as-needed inhaled corticosteroid use must be supplemented with twice daily inhaled budesonide or daily oral prednisone for a defined period as done in the study. Furthermore, as-needed, quick-relief therapy with a beta agonist should be used as defined in the NAEPP Guideline.[2]

As-needed corticosteroid therapy may be effective in carefully selected patients who understand the necessity for prompt treatment of exacerbations with quick-relief, prescribed agents. Assessment of the severity of asthma must be carefully performed so as not to underestimate patient needs. Advise patients to openly discuss their level of asthma control and treatment needs.

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Watch for further studies and the updated NAEPP guidelines in 2006.

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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