CLINICAL DECISIONS
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Treatment of Mild Persistent Asthma

This interactive feature addresses the diagnosis or management of a clinical case as informed by research published in this issue of the Journal. *A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at www.nejm.org, readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.*

CASE VIGNETTE

You are consulted by a 30-year-old white woman, who holds an administrative position in an office and has a lifelong history of asthma, about the treatment of her condition. In childhood, the patient visited her local hospital for treatment of acute asthma, but she was never admitted overnight and was discharged from the emergency department after a few "breathing treatments." Her asthma became quiescent in her late teens and remained so until 5 years ago, when after the birth of her first child, she began to note shortness of breath when recovering from exercise. At that time, she was awakened from sleep about once a month because of her asthma, but she did not need to seek emergency care for her condition. Her physician prescribed inhaled beclomethasone, two puffs (80 μg per puff) twice a day, and gave her an albuterol inhaler to use as an as-needed rescue treatment.

With this treatment, the patient's asthma has been stable for the past 4 years. Her current spirometric data are as follows: forced expiratory volume in 1 second (FEV_1), 3.16 liters (82% of the predicted value); forced vital capacity (FVC), 3.85 liters (82% of the predicted value); and the ratio of FEV_1 to FVC, 0.82. The fraction of nitric oxide in the exhaled air is 10 ppb. Skin testing has revealed substantial responses only to ragweed. She uses her albuterol inhaler two or three times a week, usually as premedication before exercise. She has no nocturnal symptoms. She has not had any unscheduled medical visits for her asthma.

The patient wonders whether she should receive less asthma treatment. She is willing to tolerate some symptoms if the treatment will be associated with fewer long-term side effects.

Which one of the following treatment options will most closely meet the patient's needs? Base your opinion on the published literature (including the articles by the American Lung Association Asthma Clinical Research Centers[1] and Papi et al.[2] in this issue of the *Journal*), your past experience, recent guidelines, and other sources of information, as appropriate.

1. **Switch the treatment such that beclomethasone and albuterol inhalers are used only when the patient has symptoms of asthma.**
2. **Switch the treatment to an oral leukotriene-receptor antagonist, plus as-needed rescue albuterol.**
3. **Switch the treatment to a corticosteroid and a long-acting β_2-agonist, in a single inhaler to be used each morning, plus as-needed rescue albuterol.**

To aid in your decision making, each of these approaches to treatment is defended by an expert in asthma therapy in the following short essays. Given your knowledge of the condition and the points made by the experts, which treatment approach would you choose? Make your choice on our Web site at www.nejm.org.

TREATMENT OPTION 1

As-Needed Use of Inhaled Beclomethasone and Albuterol

Monica Kraft, M.D.

The case vignette describes a young woman whose asthma is well controlled during twice-daily treatment with inhaled corticosteroids. We measure asthma control on the basis of the need for inhaled β_2-agonists to control asthma symptoms, the presence of daytime and nocturnal symptoms, the frequency of exacerbations of asthma, tolerance of exercise, and lung function. The patient has done well on all these measures and is

using albuterol essentially only on a preventive basis before exercise; she also has normal lung function and has not had an exacerbation in 4 years. Therefore, the "stepping down" of therapy is an appropriate management strategy and will also address the patient's concerns about long-term side effects of corticosteroids.[3]

Symptom-based therapy with inhaled corticosteroids and β_2-agonists is a relatively new approach, but it is supported in the literature.[4] It has distinct advantages for patients with mild persistent asthma that is well controlled, such as the patient in the case vignette. This group is especially prone to noncompliance, most likely owing to the intermittent nature of their symptoms.[5] As shown by Papi et al. in this issue of the *Journal*, the as-needed use of beclomethasone and albuterol (also known as salbutamol outside the United States) in a single inhaler significantly reduced the overall use of corticosteroids, yet maintained the control of asthma. The dose of beclomethasone per puff (250 μg) in that study was considerably higher than what the patient in the vignette uses (80 μg), so the degree to which the use of beclomethasone could ultimately be reduced in the patient with an as-needed approach is not known.

However, a recent study by the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute[4] showed that, in patients with mild persistent asthma, the use of as-needed inhaled corticosteroids according to a symptom-based action plan did not result in significant differences in the morning peak expiratory flow rate as compared with either twice-daily budesonide or twice-daily zafirlukast. In that study, the daily use of budesonide did improve the prebronchodilator FEV_1 (but not the postbronchodilator FEV_1) and also increased the number of symptom-free days, as compared with as-needed therapy.[4] The quality of life of patients receiving each treatment regimen was similar. Since the patient in the vignette is concerned about the long-term effects of inhaled corticosteroids and is willing to tolerate some increase in symptoms, an as-needed regimen has the greatest potential to decrease her exposure to corticosteroids while tailoring treatment directly to her symptoms.

The as-needed inhaled beclomethasone and albuterol regimen is the most appropriate choice for the patient, since current guidelines indicate that long-acting beta-agonists are not indicated for the treatment of mild persistent asthma.[6] A leukotriene modifier is an option, but it would require daily use and, at this time, it is second-line therapy to an inhaled corticosteroid for the treatment of mild persistent asthma.[6] The long-term benefits of as-needed low-dose inhaled corticosteroids are not known, since clinical trials have yet to be performed. Although the use of inhaled corticosteroids on an intermittent basis has not been specifically approved by the FDA, it makes sense for step-down therapy to be administered as a means of reducing exposure to corticosteroids. In a motivated patient who understands the risks, step-down therapy could prove useful to optimize the control of asthma symptoms. In an era in which we desire to personalize medicine, an as-needed regimen of antiinflammatory medication for well-controlled mild persistent asthma could achieve this goal in the patient, reducing exposure to corticosteroids while maintaining control of her asthma.

Dr. Kraft reports serving as a consultant to Teva Specialty Pharmaceuticals, GlaxoSmithKline, and Merck; receiving lecture fees or royalties for educational materials from Boehringer Ingelheim, GlaxoSmithKline, Merck, Elsevier, and Schering-Plough; and receiving grant support from Asthmatx, Genentech, Altana, and GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

From the Pulmonary Division, Duke Medical Center, Durham, NC.

TREATMENT OPTION 2

Oral Leukotriene-Receptor Antagonist plus As-Needed Rescue Albuterol

Elliot Israel, M.D.

The woman described in the case vignette has well-controlled mild persistent asthma. She is an optimal candidate for the use of less medicine to control her disease, but before treatment can be reduced, it is important to be sure of the goals of asthma therapy. The Guidelines for the Diagnosis and Management of Asthma of the National Asthma Education and Prevention Program suggest that these goals include decreasing the frequency of troublesome symptoms (e.g., nighttime awakenings) to twice or fewer per month, decreasing the frequency of symptoms and the as-needed use of beta-agonists (except to prevent exercise-induced symptoms) to no more than 2 days

per week, maintaining near-normal pulmonary function, reducing the frequency of recurrent exacerbations to no more than one per year, meeting the expectations of patients regarding asthma care, and minimizing or eliminating the adverse effects of therapy.[7] In the patient in the vignette, the first five goals have been met, but has the sixth?

The patient's current treatment regimen results in the use of the equivalent of approximately 100 mg of beclomethasone per year. (All doses mentioned here reflect adjustment for equivalence among different preparations of inhaled corticosteroids, according to standards of the National Asthma Education and Prevention Program.) The articles by the American Lung Association Asthma Clinical Research Centers[1] and Papi et al.[2] in this issue of the *Journal* suggest several potential means of reducing the patient's use of inhaled corticosteroids. Although there are other possibilities, this feature focuses on three treatments: the as-needed use of a combination of inhaled corticosteroids and short-acting beta-agonists (resulting in a dose equivalent to approximately 37 mg of beclomethasone per year), the once-daily use of a combination of inhaled corticosteroids and long-acting beta-agonists (resulting in a dose equivalent to approximately 45 mg of beclomethasone per year), and the daily use of a leukotriene modifier.

How is one to choose among the three options? In this case, the patient's expressed desires and her clinical history should guide us. She would prefer less therapy and fewer long-term side effects. Before the publication of the articles that appear in this issue of the *Journal*, I would have surmised from the patient's history of few to no previous exacerbations in the absence of controller therapy that it would be safe to reduce the doses of her medications. Furthermore, the articles provide evidence that, regardless of the clinical history, the current level of control of the patient's asthma puts her at minimal risk for serious asthma symptoms with any of the three treatment choices. Nonetheless, she may notice some mild differences in the control of symptoms among the three regimens. She is willing, however, to tolerate some increase in symptoms, should they occur.

She is also concerned about side effects. Although the effects of long-term inhaled corticosteroids are small, if the patient receives the current dose for 25 years, her risk of fracture may be doubled.[8] The two treatments involving corticosteroids and beta-agonists would reduce the dose of inhaled corticosteroids by two thirds as compared with her current therapy, but the relationship between bone loss and the dose of inhaled corticosteroids varies widely among patients.[8]

The patient may appear to be a candidate for as-needed controller therapy only,[4] but her symptoms with exercise caused her to seek therapy 5 years ago. Thus, it is unlikely that she will be satisfied with no therapy at all. Leukotriene modifiers address this problem. They reduce the degree of exercise-induced bronchospasm without tachyphylaxis[9] or concerns related to the use of long-acting beta-agonists alone.[10] If her symptoms are intolerable or include frequent exacerbations (both highly unlikely, given her history), the two treatments involving corticosteroids and beta-agonists could be considered. However, the regular use of a leukotriene modifier addresses this patient's concerns about the side effects of medications. It should also decrease her most bothersome symptom: exercise-induced bronchospasm. It's just what the patient ordered; the physician would do well to heed her call.

Dr. Israel reports serving as a consultant for Asthmatx, Critical Therapeutics, Genentech, Merck, Protein Design Labs, Schering-Plough, and Teva Specialty Pharmaceuticals; receiving lecture fees from Genentech and Merck; and receiving grant support from Boehringer Ingelheim, Centocor, and Merck. No other potential conflict of interest relevant to this article was reported.

From the Pulmonary and Critical Care Division, Brigham and Women's Hospital, Boston.

TREATMENT OPTION 3

Once-Daily Corticosteroid plus Long-Acting β_2-Agonist in a Single Inhaler

George T. O'Connor, M.D.

In light of the article by the American Lung Association Asthma Clinical Research Centers in this issue of the *Journal*,[1] I would switch the patient to the once-daily use of a combination inhaler containing a low-dose corticosteroid and a long-acting β_2-agonist. Although not approved by the FDA for once-daily dosing, this treatment appears to provide better asthma control than

once-daily oral montelukast and greater convenience than a twice-daily inhaled corticosteroid.

The study found that the once-daily use of a combination inhaler led to asthma control equivalent to that from the use of a twice-daily low-dose inhaled corticosteroid and superior to that from the use of oral montelukast. These findings are not surprising. Low-dose inhaled corticosteroid appears to control asthma better than oral montelukast.[11,12] Furthermore, the combination of an inhaled corticosteroid and an inhaled long-acting β_2-agonist leads to better asthma control than an inhaled corticosteroid alone.[13] In addition, the once-daily administration of inhaled corticosteroid provides a substantial proportion of the benefits of twice-daily administration.[14] This constellation of findings makes once-daily combination inhaler therapy an attractive treatment option for patients with mild persistent asthma.

Of course, efficacy must be balanced against safety. Although considerable attention has been paid to reports that the use of long-acting β_2-agonists may be associated with an increased risk of severe or fatal asthma attacks, these reports derive from studies of separate long-acting β_2-agonist inhalers rather than combination products. The use of separate long-acting β_2-agonist inhalers could lead to deaths from asthma, through either pharmacologic mechanisms or behavioral mechanisms, if patients feel better after their use and, as a result, stop using their inhaled corticosteroids or alter other behaviors. There are no data to suggest that combination inhalers containing a corticosteroid and a long-acting β_2-agonist increase the risk of severe asthma attacks or deaths as compared with other therapies.[15] A Cochrane Review of trials involving an inhaled long-acting β_2-agonist or placebo in combination with an inhaled corticosteroid showed similar rates of serious adverse events and withdrawals from treatment owing to poor asthma control over the short term.[13] The long-term use of a high-dose inhaled corticosteroid has been linked to osteoporosis, cataracts, and glaucoma, but low-dose therapy appears unlikely to increase the risk of these conditions appreciably.

Recently published guidelines do not recommend the use of a combination inhaler containing a corticosteroid and a long-acting β_2-agonist as an alternative therapy for mild persistent asthma. However, these guidelines draw heavily on expert opinion, since studies comparing alternative treatments are often lacking. Guidelines change over time and should not be viewed as rigid, especially since the results of new research — such as those reported in this issue of the *Journal* — can provide the evidence base lacking in the past.

In my clinical experience, the combination dry-powder inhaler containing a corticosteroid and a long-acting β_2-agonist, which has been available in the United States for the past 7 years, is very effective and easy for patients to use. The patient in the case vignette, whose asthma is very well controlled with the use of a twice-daily low-dose inhaled corticosteroid, appropriately desires a reduction in therapy and the minimization of long-term side effects. The results of the American Lung Association Asthma Clinical Research Centers study support the treatment of this patient with the use of a combination inhaler containing a low-dose corticosteroid and a long-acting β_2-agonist — a therapy with the advantages of convenience, optimal asthma control, and an excellent long-term safety profile.

Dr. O'Connor reports serving as a consultant to GlaxoSmithKline, Wyeth, Astellas Pharma U.S., and Sepracor. No other potential conflict of interest relevant to this article was reported.

From the Pulmonary Center, Boston University School of Medicine, Boston.

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