Going Off-Label to Treat Hard-to-Control Asthma

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Tiotropium in Asthma Poorly Controlled With Standard Combination Therapy

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Study Summary

Most asthmatic patients can be fairly well controlled by standard therapy, including regular maintenance anti-inflammatory therapy with or without the addition of a long-acting beta agonist.\footnote{1} For a minority, however, these therapies alone may be inadequate. Anticholinergic agents have not been approved for the management of asthma, nor has their use been recommended in guidelines. However, some small, short-term studies suggest that tiotropium, a long-acting anticholinergic agent approved for the management of chronic obstructive pulmonary disease (COPD), may have benefit
as an add-on to usual asthma therapy.

Two recent, prospective, replicate trials have examined the efficacy and safety of daily maintenance tiotropium delivered as a "soft mist inhaler" to patients whose asthma was not well controlled despite treatment with an inhaled glucocorticoid (> 800 mg budesonide or equivalent) plus a long-acting beta agonist. Both trials were placebo-controlled and lasted 48 weeks. Two coprimary endpoints were lung function parameters at the conclusion of the study, and secondary endpoints included morning and evening peak flow measurements, asthma symptom scores during the study, and time to the
first exacerbation of asthma.

In both trials, peak (3 hours after administration) and through lung function (24 hours after administration) improvements were significantly greater in the groups receiving tiotropium than in those receiving placebo. These improvements persisted throughout the 48 weeks of study without evidence of tachyphylaxis. The time to first exacerbation was significantly longer in the tiotropium groups, 282 days vs 226 days, corresponding to a 21% reduction of risk ($P = .03$). The asthma control scores were better in the tiotropium group, although the minimal clinically important difference was not achieved.
in either trial. In subgroup analyses, patients with worse lung function, including males and former smokers, tended to achieve more benefit from tiotropium than did other patients.

Among reported adverse events, only allergic rhinitis was more common in the tiotropium groups, occurring in 1.3% and 4.6% of patients. Serious adverse events were equal in the 2 groups and were considered not to be drug-related.

**Viewpoint**
Clinical trials performed when atropine was still being used as a bronchodilator showed that anticholinergic agents were more effective in COPD than in asthma.\[^2\] Consequently, pharmaceutical companies focused on developing anticholinergic agents for COPD. However, it was known that anticholinergic agents were effective in some asthmatic patients, and their use in clinical practice, particularly by specialists, was continuous, particularly in patients whose asthma was difficult to control. The present, well-conducted, large, long-term, replicate trials provide validation for this practice.

Poor control of asthma is an important clinical problem
that affects health as well as healthcare costs, which can be substantial when patients need to obtain emergency department care. Some patients have little awareness of the activity of their asthma until their breathing becomes so difficult that they must seek urgent care. Other asthmatics are poorly compliant with their asthma therapy for a variety of reasons. But another important group, comprising roughly 3% of all asthmatics, has severe asthma that is not well controlled despite adherence to asthma guidelines. This group has always been a challenge for the physician as well as the patient. One may be forced to consider oral corticosteroid therapy with
all its attendant adverse effects, or more drastic and expensive therapies such as anti-immunoglobulin E injections or bronchial thermoplasty.

Tiotropium has the advantage in that it is a once-a-day inhalation with a mode of administration that patients are already familiar with and, being the most commonly used long-acting bronchodilator in the world, has a well-known safety profile.

Important considerations are that it remains essential that patients have and continue to use their anti-inflammatory therapy, emphasizing the importance of compliance.
Tiotropium has not been approved for the treatment of asthma in the United States. The mode of administration of tiotropium in the study reported here, by a "soft-mist" delivery device called Respimat® (Boehringer Ingelheim Pharma GmbH & Co. KG; Ingelheim, Germany), is not available at present in the United States.

Abstract

References
