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Would this long-acting bronchodilator be better for your patient?

Tiotropium outperformed salmeterol in reducing the frequency of exacerbations in patients with moderate-to-severe COPD.

PRACTICE CHANGER

Consider adding tiotropium to the medication regimen of patients with moderate to very severe chronic obstructive pulmonary disease (COPD), as a multinational study found it to be more effective than salmeterol in preventing exacerbations.¹

STRENGTH OF RECOMMENDATION

A: Based on one well-designed randomized controlled trial.

Vogelmeier C, Hederer B, Glaab T, et al; POET-COPD investigators. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med.* 2011;364:1093-1103.

ILLUSTRATIVE CASE

A 60-year-old patient with moderate COPD and a history of frequent exacerbations comes in for a follow-up visit. She has been using albuterol and ipratropium intermittently. You want to add a longer-acting bronchodilator and wonder if tiotropium or salmeterol is more effective for reducing exacerbations.

COPD is the fourth leading cause of death in the United States.² More than 12 million Americans have been diagnosed with COPD, and it is estimated that another 12 million would have a COPD diagnosis if all smokers older than 45 years underwent spirometry.² The disorder accounts for some 16 million physician visits each year and costs the US health care system approximately \$19

billion annually, with acute exacerbations and hospitalizations representing 58% of the total.^{2,3}

Despite guidelines, COPD is often undertreated

One of the main goals of COPD treatment is to reduce the frequency and intensity of acute exacerbations, both to improve patients' quality of life and reduce health care costs. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed guidelines for effective management of COPD, which recommend long-acting bronchodilators as first-line maintenance therapy for patients whose disease is moderate to very severe.⁴

Evidence suggests that physicians frequently undertreat moderate to severe COPD, however, following national guidelines only about a quarter of the time.⁵ This is, in part, because many clinicians doubt the efficacy of COPD treatment for improving symptoms or decreasing exacerbations.^{5,6} Yet studies have shown that the long-acting bronchodilators tiotropium (an anticholinergic agent) and salmeterol (a beta2-adrenergic agonist), used with or without inhaled corticosteroids, are effective in reducing the frequency of COPD exacerbations, improving quality of life and lung function, and reducing the number of hospitalizations.⁷⁻¹⁰

Long-acting bronchodilators are therefore clearly indicated but, until recently, there was little evidence as to which one is better.

STUDY SUMMARY

Tiotropium group had fewer exacerbations ...

The Prevention Of Exacerbations with Tiotropium in COPD (POET-COPD) trial compared tiotropium with salmeterol for their ability to prevent exacerbations.¹ This was a randomized double-blind trial of 7376 patients with moderate to very severe COPD diagnosed by spirometry. Participants were recruited from 725 medical centers in 25 countries. To be eligible, they had to be ≥ 40 years, with at least a 10 pack-year history of smoking, a forced expiratory volume in 1 second (FEV1) $< 70\%$ predicted, an FEV1/forced vital capacity (FVC) $< 70\%$, and at least one exacerbation in the previous year.

Patients were randomly assigned to either the tiotropium or the salmeterol group. Those on tiotropium received a daily dose of 18 mcg through a HandiHaler device, plus a placebo with a metered-dose inhaler twice a day. Patients in the other group received 50 mcg salmeterol through a metered-dose inhaler twice daily, plus a placebo with a HandiHaler once a day. These medications were in addition to patients' current medication regimens, including inhaled corticosteroids, with this exception: Use of anticholinergics and long-acting beta-agonists was discontinued for the course of the trial.

All participants were followed for one year, with clinic visits at 2, 4, 8, and 12 months to assess for medication adherence and symptoms of exacerbation. The primary endpoint was the time to first exacerbation. This was defined as an increase in, or a new onset of, more than one symptom of COPD (ie, cough, sputum production, wheezing, dyspnea, and chest tightness), with at least one symptom lasting ≥ 3 days and leading to treatment with glucocorticoids and/or antibiotics, or hospitalization. Secondary outcomes were times to first moderate and severe exacerbations and use of steroids and antibiotics.

There were significant differences in several outcomes. The time to first exacerbation was 187 days for tiotropium vs 145 days for salmeterol, a difference of 42 days (hazard ratio [HR]=0.83; 95% confidence interval [CI], 0.77-0.90; $P < .001$). In addition, tiotropium reduced the annual number of exacerbations compared with salmeterol (rate ratio=0.89;

95% CI, 0.83-0.96; $P = .002$), with a number needed to treat (NNT) of 24 patients to prevent one moderate to severe exacerbation per year.

... and used fewer drugs

Compared with salmeterol, there was a 14% reduction in risk of a moderate exacerbation associated with tiotropium (HR=0.86; 95% CI, 0.79-0.93; $P < .001$; NNT=32) and a 28% reduction in risk of a severe exacerbation (HR=0.72; 95% CI, 0.61-0.85; $P < .001$; NNT=48). In addition, the tiotropium group had a 23% risk reduction in the use of systemic glucocorticoids (HR=0.77; 95% CI, 0.69-0.85; $P < .001$; NNT=26) compared with the salmeterol group, and a 15% risk reduction in the use of antibiotics (HR=0.85; 95% CI, 0.78-0.92; $P < .001$; NNT=31). The difference in reduction in death rates between the 2 groups was not statistically significant.

The observed differences were consistent across all major subgroups (age, sex, smoking status, and severity of COPD) of patients studied. Interestingly, patients with low BMI or very severe COPD appeared to benefit the most from tiotropium.

WHAT'S NEW

The difference between 2 agents is clear

Although national guidelines recommend long-acting bronchodilators for COPD that is moderate or worse, there have been few data to guide clinicians in determining which one to use. The findings of this study suggest that tiotropium should be our first choice. Tiotropium's once-a-day dosing is an additional benefit, as patients using it will likely have better compliance than those using twice-daily salmeterol. The data may also prompt development of a once-daily inhaled corticosteroid/long-acting anticholinergic combination.

CAVEATS

Cost, funding source

Cost may be an issue. Spiriva and Serevent, the brand names for tiotropium and salmeterol, respectively, are second-tier medications on several formularies, and tiotropium is about 45% more expensive (tiotropium=\$262,



Tell us about your use of long-acting bronchodilators by voting in our Instant Poll, which you'll find on the next page.

salmeterol=\$181 for one month's supply; www.drugstore.com, accessed January 19, 2012). There are also several long-acting beta-agonists in development that will be dosed once daily; once they're approved, tiotropium's once-a-day dosing may no longer be seen as an advantage.

It is also worth noting that this trial was supported by Boehringer Ingelheim and Pfizer, which jointly market Spiriva.

Finally, smoking must be addressed. Strongly encouraging patients to kick the habit is still the most important intervention we can make in helping to improve the quality of life, and survival, of patients with COPD.

CHALLENGES TO IMPLEMENTATION

COPD guidelines need updating

There are no major challenges to incorporating this recommendation into clinical

practice; the key challenge lies in diagnosing COPD and adequately monitoring and helping patients manage the disease.

Current guidelines do not distinguish between the efficacy of long-acting bronchodilators, but findings from this study are important enough to change future versions of national guidelines. The GOLD committee is due to release a new guideline report soon, and will likely update its recommendations at that time. **JFP**

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INSTANT POLL

Do you use a long-acting bronchodilator as first-line maintenance therapy for patients with COPD that is moderate to severe?

Always

Sometimes, depending on the frequency and severity of exacerbations

Rarely or never

Other _____

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