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Consider adding this drug to fight COPD that's severe

Daily use of azithromycin, in conjunction with the usual COPD regimen, has been found to reduce acute exacerbations in patients with moderate to severe disease.

PRACTICE CHANGER

Consider prescribing daily azithromycin for patients with chronic obstructive pulmonary disease (COPD) and a history of exacerbations—but do a careful risk-benefit analysis first.[1]

STRENGTH OF RECOMMENDATION

B: Based on one well-designed double-blind, randomized controlled trial (RCT).

Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365:689-698.

ILLUSTRATIVE CASE

A 65-year-old man with a history of moderate to severe COPD schedules an appointment soon after discharge from the hospital—his second hospitalization for COPD exacerbations in 4 months. The patient uses inhaled glucocorticoids, a long-acting beta-agonist (LABA), and a long-acting anticholinergic. Should you add a macrolide to his medication regimen?

Acute exacerbations of COPD—the third highest cause of death in the United States[2]—have a major effect on quality of life, often resulting in repeat trips to the emergency department (ED) and numerous hospitalizations, office visits, and days lost from work. According to a new study that used 2006 data, there were 1.25 million hospitalizations for COPD exacerbations that year, with health care costs of $11.9 billion.[3] Preventing exacerbations and the associated morbidity and mortality is a major challenge that primary care physicians face.

Can a macrolide help?

Corticosteroids, long-acting beta-agonists (LABAs), and the anticholinergic tiotropium are known to reduce COPD exacerbations,[4,5] but what about antibiotics? A Cochrane meta-analysis of 9 RCTs that assessed antibiotic use for COPD found that it did not decrease the number of exacerbations. Notably, however, macrolides were not used in any of the studies.[6]

Macrolides are known to have anti-inflammatory, antibacterial, and immunomodulatory properties that reduce pulmonary exacerbations in other chronic lung diseases. A recent meta-analysis found that patients with cystic fibrosis have fewer pulmonary exacerbations when they take azithromycin 3 times a week.[7]

Small studies of the effect of macrolides on the frequency of COPD exacerbations have had conflicting results.[8,9] The larger study detailed here evaluated the ability of daily azithromycin therapy to reduce COPD exacerbations.

STUDY SUMMARY

Daily dose led to fewer exacerbations

This double-blind RCT included close to 1150 participants from 12 US academic health cen-

ters, randomly assigned to receive azithromycin 250 mg daily or placebo, in addition to their usual care. (About 10% of patients in both groups died, withdrew, or were lost to follow-up.)

To be included, patients had to be ≥40 years old and have a clinical diagnosis of COPD, defined as a smoking history of 10 pack-years or more, a decreased forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio, and a decreased FEV1 after bronchodilation. In addition, participants had to be on long-term oxygen or have used systemic steroids within the previous year or have had an ED visit or hospital admission for COPD during that time frame. Exclusion criteria included a history of asthma, a resting heart rate >100 beats per minute, a prolonged corrected QT interval (QTc) on electrocardiogram or the use of a medication that might prolong QTc, and a documented hearing impairment.

At baseline, participants were similar in basic demographics, COPD severity, smoking history, and medication use: 49% of those in the azithromycin group and 46% of the placebo group were taking a combination of inhaled corticosteroids, LABAs, and a long-acting anticholinergic medication.

The primary outcome was the time to the first COPD exacerbation. This was defined as ≥3 days with 2 or more COPD symptoms—new onset or worsening cough, dyspnea, sputum production, chest tightness, or wheezing—for which antibiotics or steroids were required. Secondary outcomes were quality-of-life measurements on the St. George's Respiratory Questionnaire (SGRQ) and the Medical Outcomes 36-item Short Form Health Survey (SF-36). Nasopharyngeal swabs were done every 3 months to check for colonization and resistance. Hearing was assessed with audiometry at the time of enrollment, and again at 3 and 12 months. All patients were followed for a year, with monthly telephone calls or clinic visits, to determine if an exacerbation had occurred in the previous month.

The median time to the first exacerbation in the azithromycin group was 266 days (95% confidence interval [CI], 227-313) vs 174 days (95% CI, 143-215) in the placebo group; $P<.001$. Frequency of acute exacerbations was 1.48 per patient-year for the azithromycin group compared with 1.83 for the placebo group (relative risk=0.83; 95% CI, 0.72–0.95; $P=.01$). The number needed to treat to prevent one acute exacerbation in a one-year period was 2.86.

There was no significant difference in the SGRQ and SF-36 scores for the azithromycin vs the placebo group. There was a small reduction in unscheduled office visits (0.11 per patient-year; $P=.048$) in the azithromycin group, and a decrease in hospitalization that was not statistically significant.

Azithromycin group had higher rates of adverse effects

Nasopharyngeal cultures from participants who became colonized during the course of the study found macrolide resistance in 81% of those in the azithromycin group vs 41% of the placebo group ($P<.001$). Twenty-five percent of patients in the azithromycin group developed measurable hearing loss, compared with 20% of those on placebo ($P=0.04$; number needed to harm=20).

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WHAT'S NEW?

A better understanding of benefits and risks

This study shows that the addition of azithromycin (250 mg/d) to standard COPD treatment decreases the number of exacerbations, but does little to reduce hospital admissions. It also highlights the adverse effect profile of azithromycin and the importance of using the antibiotic only for carefully selected patients.

CAVEATS

Macrolide resistance is a key concern

Twenty-five percent of the azithromycin group had documented hearing loss—an additional one in 20 compared with patients in the placebo group. More importantly, there was an increase in the prevalence of macrolide-resistant respiratory pathogens in patients on daily azithromycin. The long-term impact of daily azithromycin on antibiotic resistance is unknown, both for patients themselves and the community at large.

CONTINUED

Physicians will have to assess the benefit of a decrease in COPD exacerbations (approximately one every 3 years) vs the risk of an increase in hearing problems and macrolide resistance. A sensible approach would be to reserve daily use of azithromycin for patients with a history of multiple exacerbations, who potentially have more to gain.

CHALLENGES TO IMPLEMENTATION

There are none

There are no major challenges to implementation aside from the cost, which would be approximately $1200 per year (azithromycin 250 mg [30 tablets] at $98.99 per month).[10] JFP

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