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Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, Make B, Marchetti N, Martinez FJ, Madinger NE, McEvoy C, Niewoehner DE, Porsasz J, Price CS, Reilly J, Scanlon PD, Sciurba FC, Scharf SM, Washko GR, Woodruff PG, Anthonisen NR; COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.

Chronic obstructive pulmonary disorder, COPD, has a prevalence of approximately 10% in people over the age of 40 and an estimated 24 million adults in the United States suffer from symptoms of COPD. Acute exacerbations of chronic obstructive pulmonary disease result in an increased risk of death, decreased quality of life, and a more rapid decline in lung function than those patients with COPD who do not suffer from exacerbations.

This study was a randomized trial that recruited patients from 17 different sites to determine whether daily azithromycin decreased the frequency of acute exacerbations in patients with COPD. The study was a prospective, parallel-group, placebo-controlled trial that took place from March 2006 through June 2010. There were 1142 participants, 570 in the azithromycin group and 572 in the placebo group. Participants in the azithromycin group were to take 250mg by mouth daily for one year; participants in the placebo group also took a similar appearing tablet for one year.

Participants in both groups were at least 40 years of age, had a clinical diagnosis of COPD confirmed by pulmonary function testing, had received systemic glucocorticoids within the previous year, or used continuous supplemental oxygen, or had gone to the emergency department or been admitted to the hospital for an acute COPD exacerbation. The participants were not included in the study if they had an acute exacerbation within four weeks prior to joining the study. Participants were excluded from the study if they had asthma, a resting heart rate greater than 100 beats per minute, a prolonged QT interval (>450msec), hearing impairment confirmed by audiometric testing, or were also using drugs that could prolong the QT interval or were associated with torsades, with the exception of amiodarone. The breakdown of participants had approximately 26% at GOLD stage II, 40% GOLD stage III, and 34% GOLD stage IV at the time of the study in both the placebo and azithromycin groups.

Primary outcome of the study was the time to the first acute COPD exacerbation, which was defined as: increased or new onset of either cough, sputum, wheezing, chest tightness or dyspnea of at least three days requiring antibiotics or systemic steroids. The date of the exacerbation was documented via clinic visit or telephone contact and was recorded as the date treatment was prescribed.

Secondary outcomes of the study were quality of life determined by two different questionnaires, nasopharyngeal colonization of Staphylococcus aureus, Streptococcus pneumonia, Haemophilus influenza or Moraxella, and adherence to the drug regimen. Nasal swabs were done at enrollment and every three months during the study looking for colonization and macrolide resistant bacteria.

Results of the study showed 1641 acute COPD exacerbations, 741 in the azithromycin group and 900 in the placebo group. There was a significant difference in the time to first exacerbation between the two groups with a median time to the first exacerbation of 266 days in the azithromycin group and 174 days in the placebo group. Frequency of exacerbations was found to be significantly lower in the azithromycin group and the number needed to treat to prevent one exacerbation would be approximately three patients.

Secondary outcomes, however, had less significance. Although statistically significant improved quality of life per questionnaire the group did not meet the minimum goal they had set prior to the start of the study to establish improved quality of life. There proved to be no significant difference in the rate of adherence to azithromycin compared to placebo. There was an increase in hearing deficits in the azithromycin group by 5% when compared with placebo. Unfortunately all patients who suffered a hearing deficit were to be taken off azithromycin immediately, which did not occur in all patients due to a protocol error. There was also no significant difference seen in the rate of death between the two groups, which demonstrated three percent in the azithromycin group and four percent in the placebo group.

Regarding colonization of organisms in the nasopharynx, those patients not colonized at the beginning of the study who were placed on azithromycin had a decreased incidence of new colonization compared to those on placebo, and this was found to be significant with a $P < 0.001$. However, in those people without colonization prior to the study who then became colonized during the study there was an increase in resistance to macrolides versus the placebo group, (81 percent vs. 41 percent) and this was also significant. However, there was no evidence showing that the exacerbations occurring in the azithromycin group were due to the new macrolide resistant bacteria. Those people already colonized prior to the study had no significant difference in the prevalence of resistance to macrolides, but this finding was not statistically significant.

The data from this study looks promising. We know that macrolides have immune modulatory and anti-inflammatory effects in addition to antibacterial effects, the former of which are likely offering much of the benefit observed in this study. However, it is still too soon to say that this should become the next step in preventing COPD exacerbations. Azithromycin is used in cystic fibrosis patients with bronchiectasis 500mg by mouth three times a week to help prevent exacerbations, but we also see an increase in multidrug resistant bacteria in that population. This study does not follow patients long enough out to see if a similar

result will occur with COPD. A larger study with longer follow up targeting GOLD stage III and IV participants already on appropriate medical management may be of benefit. In this study it was difficult to tell if those participants involved were already on appropriate medical management and receiving standard of care and if not would there have been similar results from implementing that without the risk of worsening macrolide resistance. That being said, for my own patient population, I would consider using azithromycin for COPD exacerbation prophylaxis in the patient that is suffering from severe disability from repeat COPD exacerbations, is already on optimal medical management and even on optimal management is still requiring frequent hospitalizations for acute exacerbations of COPD.

Rebecca Zaner, D.O.

Manoj Mathew MD, FCCP, MCCM
Associate Editor, Pulmonary Journal Club