

Long-term macrolide therapy in chronic obstructive pulmonary disease

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Exacerbations of chronic obstructive pulmonary disease (COPD) are characterized by worsening respiratory symptoms, which are almost always accompanied by an increase in airway inflammation.¹⁻³ The majority of these exacerbations are caused by microbial infection.⁴ By current estimates, about 50% of exacerbations are caused by bacteria, either alone or in combination with viruses.⁴ Before 1970, multiple attempts were made to test the hypothesis that prophylactic antibiotics can reduce the frequency of COPD exacerbations. Unfortunately, the trials were small, with differing methods and antibiotic choices. Most used antibiotics that would likely not be effective today, given changes in antibiotic susceptibilities of bacterial pathogens. A systematic review of these trials did show a small reduction in the frequency of exacerbations (odds ratio [OR] 0.91, 95% confidence interval [CI] 0.84–0.99).⁵ However, because the effect was modest and because of methodologic limitations and concerns about antibiotic resistance, these results cannot be applied in the present-day care of patients with COPD.

A resurgence of interest in the use of prophylactic antibiotics in COPD has emerged over the past decade, with an emphasis on the use of macrolides. It might be assumed that the antimicrobial properties of macrolides were the premise for studying whether these drugs can be used to prevent exacerbations, given that they

are used to treat exacerbations on this basis. In fact, this use of macrolides has been based more on their potential anti-inflammatory and immunoregulatory effects, which have been shown in both in vitro experimental models and other inflammatory lung diseases. In this paper, we review the evidence for benefit and potential harms of long-term prophylactic macrolide therapy in reducing COPD exacerbations. This evidence is derived (using the search strategy outlined in Box 1) primarily from a few randomized trials, dominated by one large recent trial.

What biological actions of macrolides are relevant to COPD?

It is likely that the antibacterial effects of macrolides contribute to their effects on exacerbations in COPD. Patients with COPD who have colonization by pathogenic bacteria have higher levels of airway inflammation than those without such colonization.⁶ Hence, eradication or suppression of chronic bacterial colonization by macrolides could reduce infection-related airway inflammation, make the airway milieu less hospitable to infection with new strains of bacteria and viruses, and thus reduce the likelihood of exacerbation.

The four major bacterial pathogens involved in exacerbations of COPD are nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*.⁴ Almost all strains of *H. influenzae* and *M. catarrhalis* are susceptible to clarithromycin and azithromycin,⁷ as are the majority of strains of *S. pneumoniae*.⁸

P. aeruginosa is not clinically susceptible to macrolides. However, macrolides have indirect activity against *P. aeruginosa* through suppression of virulence factors, which may contribute to their beneficial effects in reducing exacerbations.⁹ Macrolides suppress the synthesis of elastase, lecithinase and pyocyanin, and they alter

KEY POINTS

- Macrolides have immunomodulatory as well as antibacterial effects in chronic obstructive pulmonary disease (COPD).
- In selected patients with severe COPD and frequent exacerbations, long-term macrolide prophylaxis reduces the frequency of exacerbations.
- Concerns that remain regarding adverse events and increased microbial resistance to macrolides must be addressed in future studies.
- Careful patient selection and optimization of COPD management are essential before initiation of macrolide prophylaxis.

the structure of *Pseudomonas* endotoxin (lipopolysaccharide). The motility of *P. aeruginosa* is reduced by a decrease in flagellin production, and biofilm formation is inhibited through interference with the production of alginate and quorum signalling.^{9,10}

However, it is probable that immunomodulatory effects are responsible for at least a part of the actions of macrolides in COPD. In vitro cell culture and animal models have shown that macrolides possess potent anti-inflammatory and immunomodulatory properties (Box 2).^{11,12} Relative to alveolar macrophages from healthy controls, those from patients with COPD have decreased ability to phagocytose apoptotic cells (efferocytosis)¹⁴ and pathogenic bacteria.¹⁵ Azithromycin reverses this deficit in efferocytosis¹⁴ and improves the ability of macrophages from patients with COPD to phagocytose bacteria.¹⁶ Furthermore, macrolides were successful in preventing exacerbations and improving lung function in cystic fibrosis^{17,18} and improving survival in diffuse panbronchiolitis.¹⁹ In these two airway diseases, the major pathogen is *P. aeruginosa*, against which macrolides are decidedly ineffective in conventional antimicrobial terms. In addition, two trials of erythromycin prophylaxis in COPD used doses lower than required for antimicrobial effects, but the drug was nevertheless beneficial.^{20,21} However, measurements of pro-inflammatory cytokines in patients with COPD enrolled in macrolide treatment trials have yielded conflicting results. Therefore, there is still no clear evidence that the benefits of macrolides in COPD are related to these immunomodulatory effects.

Gastroesophageal reflux has been shown to be a risk factor for increased frequency of exacerbation.²² Macrolides improve gastric emptying and reduce gastroesophageal reflux,^{23,24} and it is tempting to speculate that these effects contribute to a reduction in COPD exacerbations.

What are the potential benefits of long-term macrolide therapy in COPD?

Four randomized trials have compared a macrolide with placebo for preventing COPD exacerbations (Table 1). The first three recruited small numbers of patients and thus had low power to detect meaningful clinical benefits and risks.^{20,21,25} Despite this limitation, two of the trials reported significant reduction of exacerbations in the macrolide group.^{20,21}

More recently, Albert and colleagues²⁶ conducted a multicentre randomized controlled trial

comparing azithromycin 250 mg daily with placebo for 12 months in 1142 patients with COPD who were considered at high risk for exacerbation (defined as use of systemic steroids within the previous year, use of continuous supplemental oxygen or history of hospital admission for exacerbation in the preceding 12 months). Excluded were patients with a diagnosis of asthma, resting tachycardia, prolonged corrected QT (QTc) interval on electrocardiography, medications known to increase the QTc interval or hearing impediment. Azithromycin prolonged the median time to first exacerbation, the study's primary end point (266 v. 174 days, $p < 0.001$) and reduced the rate of exacerbations (hazard ratio [HR] 0.73, 95% CI 0.63–0.84). Quality of life at the end of one year, as assessed by the St. George's Respiratory Questionnaire, showed significantly greater improvement with azithromycin (2.8 ± 12.8 v. 0.6 ± 11.4 units; $p = 0.004$), but the mean change was less than the minimal clinically important difference for this measure (4 units). Unscheduled office visits were significantly fewer in the

Box 1: Evidence used in this review

We searched the MEDLINE database (for the period 2002 to 2013) using the following medical subject headings (MeSH): "macrolides" or "azithromycin" or "erythromycin" or "clarithromycin" and "lung disease." We limited the search to English-language articles involving human subjects for which an abstract was available. Of 496 articles initially identified, 120 were found to be relevant, of which 34 are included in this article.

Box 2: Anti-inflammatory and immunomodulatory effects of macrolides^{11,12}

Effects of macrolides on neutrophils:

- Accumulate in leukocytes at levels higher than in serum
- Inhibit neutrophil adhesion and migration to sites of inflammation
- Decrease the oxidative burst

Effects of macrolides on alveolar macrophages:

- Inhibit activation of transcription factor NF- κ B, which controls the expression of many inflammatory cytokines, chemokines, immune receptors and cell-surface adhesion molecules
- Decrease production of major cytokines involved in initiating the inflammatory response (TNF- α and IL-1)

Effects of macrolides on airway epithelial cells:

- Reduce activation of transcription factors AP-1 (transcription factor involved in activation of genes coding for cytokines involved in inflammatory response) and NF- κ B
- Decrease production of IL-6 and IL-8 in response to *Haemophilus influenzae*, thus reducing neutrophil chemotaxis to the site of infection
- Decrease secretion and viscosity of mucin
- Improve frequency of ciliary beating
- Promote epithelial integrity and transepithelial resistance by changing processing of tight junction proteins (azithromycin only)¹³

Note: AP-1 = activator protein-1, IL = interleukin, NF- κ B = nuclear factor kappa-light-chain-enhancer of activated B cells, TNF- α = tumour necrosis factor α .

azithromycin group (HR 0.85, 95% CI 0.74–0.98), but rates of hospital admission did not differ (HR 0.94, 95% CI 0.76–1.15).

What are the potential harms of long-term macrolide therapy in COPD?

Macrolides were generally well tolerated in the four studies cited above. Albert and colleagues²⁶ observed no differences in rates of death or adherence with study medications. More of the patients taking azithromycin had a significant decrease in audiometry scores than was the case among patients taking placebo (25% v. 20%, *p* = 0.004; number needed to harm 20). Hearing loss, both reversible and irreversible, has been reported as an adverse effect of macrolides.^{27,28} The possibility that the frequency and severity of this adverse event might increase with even longer courses of azithromycin is a concern.

Because macrolides increase the QTc interval and also increase the chance of torsades de pointes, another concern relates to adverse cardiovascular events and increased mortality, a possibility raised in a recent publication by Ray and colleagues.²⁹ Using the Tennessee Medicaid database, these investigators compared patients who took azithromycin for five days (about

380 000 prescriptions) with a propensity-matched sample of about 1.4 million patients who took no antibiotics. Patients taking azithromycin had a greater risk for cardiovascular-related death (HR 2.88, 95% CI 1.79–4.63) and death from any cause (HR 1.85, 95% CI 1.25–2.75) than patients taking no antibiotics. This increase in risk was most pronounced among patients who were at high risk of cardiovascular disease. Given the observational study design, uncontrolled confounding factors such as sex and pre-existing cardiac risks might have influenced the results.

Divergent findings were subsequently published in another retrospective cohort study involving patients in the Danish national health registry.³⁰ More than one million health visits with prescription of azithromycin were matched (by propensity scores, to control for baseline differences) with a similar number of visits without prescription of antibiotics and with about seven million visits with prescription of penicillin V. Although there were more deaths from cardiovascular causes in the azithromycin group than in the nonantibiotic group (rate ratio 2.85, 95% CI 1.13–7.24), this rate was not significantly different from the rate in the penicillin V group (rate ratio 0.93, 95% CI 0.56–1.55). This result suggests that the difference in cardiovascular deaths was related to other characteristics, such as comorbidities, among the patients receiving

Table 1: Summary of randomized trials of prophylactic macrolide therapy in COPD

Reference	Design	No. of patients	Intervention	Results
Suzuki et al. ²¹	Prospective, open-label, randomized	109, any severity of COPD	Erythromycin 200–400 mg daily v. riboflavin for 12 mo	Significant reduction in common colds (1.24 ± 0.07 v. 4.54 ± 0.02 for erythromycin and riboflavin groups; <i>p</i> < 0.001) and exacerbations (RR for control group 4.71, 95% CI 1.53–14.5)
Banerjee et al. ²⁵	Prospective, double-blind, randomized	67, moderate to severe COPD	Clarithromycin 500 mg daily v. placebo for 3 mo	Significant improvement in symptom domain of SGRQ (mean difference 10.2, 95% CI 1.6–18.7); no significant difference in SGRQ score* or exacerbation frequency (5 v. 3 in clarithromycin and placebo groups; <i>p</i> = 0.2).
Seemungal et al. ²⁰	Prospective, double-blind, randomized	109, moderate to severe COPD	Erythromycin 250 mg daily v. placebo for 12 mo	Significant reduction in exacerbation frequency (rate ratio 0.648 [95% CI 0.489–0.859] for erythromycin v. control group); no difference in sputum markers of inflammation (IL-6, IL-8, myeloperoxidase)
Albert et al. ²⁶	Prospective, double-blind, randomized	1142, moderate to very severe COPD (GOLD stages II–IV)	Azithromycin 250 mg daily v. placebo for 12 mo	Significant reduction in exacerbation frequency (HR 0.73, 95% CI 0.63–0.84); increase in median time to next exacerbation (266 v. 174 d for azithromycin and placebo groups; <i>p</i> < 0.001); significant improvement in SGRQ (2.8 ± 12.8 v. 0.6 ± 11.4 units, <i>p</i> = 0.004); reduction in unscheduled office visits (HR 0.85, 95% CI 0.74–0.98); no significant difference in rates of hospital admission (HR 0.94, 95% CI 0.76–1.15)

Note: CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, IL = interleukin, RR = relative risk, SGRQ = St. George's Respiratory Questionnaire.

*Scores range from 0 to 100, with higher scores indicating worse quality of life.

antibiotics, rather than a specific risk associated with azithromycin.

Finally, Albert and colleagues²⁶ observed no difference in cardiovascular adverse events or mortality, in spite of the considerable exposure to macrolides in their study. This result may be related to careful patient selection, with exclusion of patients who had prolonged QTc (and those taking other medications known to prolong QTc), as well as to differences in design and sample size. The sample size in the randomized study by Albert and colleagues²⁶ was much smaller than sample sizes in the large observational studies described above,^{29,30} and smaller sample size reduces the power to detect infrequent events.

In view of these conflicting findings, caution should be exercised in the use of azithromycin for patients with known cardiac disease (see Box 3). We recommend performing baseline electrocardiography to ensure that the QTc interval is not prolonged, as well as baseline audiometry. Periodic audiometric evaluations are also prudent while the patient is receiving treatment. For example, in the study by Albert and colleagues,²⁶ audiometric evaluations were performed at the start of treatment, at 3 months and at 12 months.

Does long-term macrolide therapy contribute to antibiotic resistance?

In patients with COPD, intermittent use of macrolides to treat exacerbations has been associated with isolation of macrolide-resistant strains of *S. pneumoniae* from sputum.³¹ Albert and colleagues²⁶ observed an increase in the incidence of macrolide-resistant nasopharyngeal bacteria among patients receiving azithromycin. In that study, nasopharyngeal swabs were used to evaluate respiratory colonization, and swabs were obtained for about 85% of patients. The rates of colonization by *Staphylococcus aureus*, *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* did not differ between the groups at the start of the study. By the end of the study period, significantly fewer patients in the azithromycin group had colonization with the same pathogens. However, among patients in the azithromycin group with occurrence of colonization during the study period, the chance of azithromycin resistance in the pathogens isolated was significantly higher ($p < 0.001$). In other words, when patients on long-term azithromycin acquired new nasopharyngeal bacteria, those bacterial strains were more likely to be resistant to azithromycin.

Previous epidemiologic studies have clearly shown an association between use of macrolides

in the community and prevalence of macrolide-resistant *S. pneumoniae*. From 1993 to 1999, macrolide prescriptions increased by 13% in the United States, with an especially steep increase (by 320%) among children under five years of age. The rate of macrolide resistance in *S. pneumoniae* isolates increased from 10.6% to 20.4% over the same period.³² In Israel, isolation of macrolide-resistant *S. pneumoniae* among children increased during the winter months, the same season when macrolide use increased among these patients.³³ In 2005–2006, 35.3% of *S. pneumoniae* in the US was resistant to macrolides.⁸ Prolonged macrolide use in a large group of patients with COPD could lead to loss of a useful antibiotic class for treatment of acute respiratory infections, not only among the patients who receive the treatment but also in the wider community.

Patients who need antibiotics for a respiratory tract infection while they are receiving macrolide prophylaxis (including exacerbation, pneumonia or sinusitis) would be best treated with a nonmacrolide antibiotic, because of concerns about infection with a macrolide-resistant bacterial strain.

Unanswered questions

Whether intermittent azithromycin prophylaxis (250 mg three times a week) would be as effective as daily dosing in preventing exacerbations is unknown. The intermittent regimen is effective in cystic fibrosis³⁴ and is our preferred starting regimen, with transition to daily dosing if intermittent dosing appears ineffective.

Although generally safe and effective, macrolides have the potential for adverse effects and

Box 3: Selection criteria for azithromycin prophylactic therapy in COPD^{20,26}

Patients likely to benefit from azithromycin prophylaxis:

- Moderate to very severe COPD (GOLD stage II = moderate, stage III = severe, stage IV = very severe)
- At least two exacerbations treated with antibiotics or systemic steroids in the past year OR at least one exacerbation that resulted in admission to hospital
- Management of COPD already optimal (i.e., long-acting bronchodilators, inhaled steroids, phosphodiesterase 4 inhibitors)
- Compliant with current therapy and using proper inhaler technique

Criteria for excluding patients from consideration for azithromycin prophylaxis:

- Prolonged QTc interval on electrocardiography (> 450 ms) OR receiving drug therapy that prolongs QTc interval
- Unstable OR uncontrolled cardiovascular disease (congestive heart failure, angina pectoris)
- Hearing impairment documented previously OR apparent on audiometry

Note: COPD = chronic obstructive pulmonary disease, GOLD = Global Initiative for Chronic Obstructive Lung Diseases.

carry societal implications for increased microbial resistance. Careful selection of patients suitable for long-term macrolide therapy is vital to maximize the benefits and minimize the risks. Our suggested criteria for patient selection, presented in Box 3, are based on the inclusion and exclusion criteria of the studies by Albert and colleagues²⁶ and Seemungal and associates,²⁰ as well as our own personal experience. Although Albert and colleagues²⁶ did not find that other treatments for COPD influenced the potential benefit of azithromycin therapy, we feel it is prudent to use more established therapies for patients with COPD, reserving long-term macrolide treatment for those who continue to suffer exacerbations.

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