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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Which patients with respiratory disease need long-term azithromycin?

A: Azithromycin is prescribed for a variety of acute respiratory and nonrespiratory infections. However, it is also used in several chronic respiratory diseases.

MECHANISM OF ACTION

Macrolide antibiotics like azithromycin inhibit bacterial growth and replication by interrupting protein synthesis. But azithromycin also has immunomodulatory properties.[1]

In the acute phase of inflammation, azithromycin exerts an initial neutrophil degranulation effect and enhances the oxidative response that is primed by particulate stimulus, which could facilitate its antibacterial effects. In the late phase, it down-regulates the oxidative burst and increases apoptosis of neutrophils to promote healing without compromising immunity. Azithromycin also attenuates airway mucus hypersecretion, improves ciliary function, and promotes pulmonary epithelial cell healing.[2,3]

Collectively, these effects make the drug effective in many chronic inflammatory lung conditions (**Table 1**).

CYSTIC FIBROSIS

Cystic fibrosis is a genetic disease affecting many organs, but its effect on the upper and lower airways has the greatest impact on quality of life and survival. Impaired mucociliary clearance and repeated respiratory infections contribute to chronic inflammation and a progressive decline in lung function.[4,5]

A 2012 Cochrane review of 5 studies in 549 patients found that, compared with those taking placebo, patients taking azithromycin 250–500 mg 3 times a week had improvement in forced expiratory volume in 1 second (FEV_1). The mean difference at 6 months was 3.97% (95% cofidence interval [CI] 1.74–6.19). Patients on azithromycin were free from pulmonary exacerbation approximately twice as long as patients on placebo (odds ratio 1.96, 95% CI 1.15–3.33).[6,7]

The Cystic Fibrosis Foundation recommends long-term azithromycin therapy to improve lung function and reduce exacerbations in patients age 6 or older who have persistent *Pseudomonas aeruginosa* airway cultures (level of evidence: fair).[8]

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis, or diffuse chronic inflammatory bronchiolitis and sinusitis, is seen mainly in patients of Asian descent.[9] In the past, the mortality rate was greater than 90%, but between 1970 and 1979 the 10-year survival rate increased by more than 40% with chronic macrolide therapy, ie, with erythromycin.[10,11]

Later retrospective studies of azithromycin 500 mg 3 times a week showed results comparable to those with erythromycin, with improvement in symptoms, lung function, arterial partial pressure of oxygen, and radiologic findings, as well as fewer adverse effects.[12] These benefits justify the current recommendation for azithromycin as the mainstay of therapy in diffuse panbronchiolitis.

BRONCHIOLITIS OBLITERANS SYNDROME

Bronchiolitis obliterans syndrome is an airflow limitation that arises without infection or imaging evidence of bronchiolitis in patients who received allogeneic hematopoietic stem

Long-term use should be individualized, weighing benefits against risks and monitoring for adverse effects

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TABLE 1

Indications for azithromycin in respiratory conditions

Antibacterial indications
Pharyngitis, tonsillitis (with penicillin allergy)
Acute exacerbation of chronic bronchitis
Community-acquired pneumonia
Prevention of *Mycobacterium avium* complex (and part of treatment regimen)
Immunomodulatory indications
Cystic fibrosis
Diffuse panbronchiolitis
Posttransplant bronchiolitis obliterans syndrome
Non-cystic fibrosis bronchiectasis
Chronic obstructive pulmonary disease

cell or lung transplant. It occurs in 50% of lung transplant recipients as a form of chronic graft rejection and in 6% to 20% of allogeneic stem cell transplant recipients as a manifestation of chronic graft-vs-host disease.[13,14]

Azithromycin has been used in its management. A meta-analysis of lung transplant recipients found a significant improvement in the survival rate and overall lung function after an average of 7 months of treatment with azithromycin, with a mean increase in FEV_1 of 8.8% (95% CI 5.1–12.47, $P < .001$).[14] The evidence currently supports long-term azithromycin 250 mg 3 times a week after lung transplant to reduce any decline in lung function and to lower the mortality rate.[14,15]

Studies have shown that azithromycin prophylaxis can reduce acute exacerbations of COPD

In allogeneic stem cell transplant recipients, the evidence for long-term azithromycin treatment is sparse. A recent prospective multicenter study evaluated the effect of an azithromycin-based regimen (fluticasone, azithromycin, and montelukast, plus a steroid pulse) in stem cell recipients with bronchiolitis obliterans syndrome during the first 3 months after diagnosis. In the treated group, 6% had a drop in FEV_1 of more than 10% at 3-month follow-up compared with 40% of historical controls (95% CI 1%–19%, $P < .001$). Also, treatment resulted in a 50% reduction in the dose of systemic steroids and a substantial improvement in functional status.[16]

Given the limited options in the management of these patients and until further studies are available, azithromycin 3 times weekly is suggested.

NON-CYSTIC FIBROSIS BRONCHIECTASIS

Non-cystic fibrosis bronchiectasis is a chronic inflammatory lung condition characterized by irreversible dilation of the bronchi and bronchioles due to a variety of causes including recurrent or old infection, immunodeficiency, autoimmune conditions, and connective tissue disease; it can also be idiopathic.[17]

Altenburg et al,[18] in a randomized, double-blind, placebo-controlled trial, found that azithromycin 250 mg 3 times a week for 12 months reduced the number of exacerbations from a median number of 2 per patient with placebo to 0 per patient with azithromycin ($P < .001$). At 3 months, the FEV_1 as a percent of predicted had increased by 1.03% in the azithromycin group and decreased by 0.10% in the placebo group ($P = .047$). The number needed to treat with azithromycin to maintain clinical stability was 3.0.

Wong et al[19] randomized patients to receive azithromycin 500 mg 3 times a week or placebo for 6 months. The rate of exacerbations was 0.59 per patient in the azithromycin group and 1.57 per patient in the placebo group ($P < .0001$). The FEV_1 remained unchanged from baseline in the azithromycin group while decreasing in the placebo group, but the difference was not significant.

EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a major cause of death, poor quality of life, and healthcare expenditures.[20] Prevention is therefore of the utmost importance.

Several studies have shown that azithromycin prophylaxis can reduce acute exacerbations of COPD. A recent meta-analysis showed that long-term macrolide prophylaxis significantly reduced exacerbations compared with rates in controls (risk ratio = 0.70,

95% CI 0.56–0.87, $P < .01$) and increased the median time to first COPD exacerbation by more than 90 days ($P < .01$).[21] Long-term azithromycin therapy may be considered in selected patients who have frequent exacerbations despite optimal maintenance inhaler therapy.

PROPHYLAXIS IN IMMUNODEFICIENCY

Disseminated *Mycobacterium avium* complex (MAC) is an opportunistic infection most commonly occurring in patients with acquired immunodeficiency syndrome with CD4 counts below 50 cells/μL.[22,23]

In a double-blinded, randomized trial, patients who received azithromycin had a 47% reduction in the incidence of MAC infection.

Given the long half-life of azithromycin, it is effective with once-weekly dosing of 1,200 mg.[23] Ideally, patients are placed on a prophylactic agent for disseminated MAC infection until the CD4 count reaches 100 cells/μL and remains at or above this level for 3 consecutive months.[24]

ADVERSE EFFECTS AND PRECAUTIONS

Long-term azithromycin therapy may produce bacterial resistance; the risk has been estimated at 2.7 times greater in patients who are on long-term azithromycin treatment.[25] Also, patients at risk for MAC infection, such as those with cystic fibrosis, should be screened for it before starting treatment in order to prevent resistance to azithromycin.

The US Food and Drug Administration warns that azithromycin can lead to a prolonged corrected QT interval and potential fatal arrhythmias such as torsades de pointes. Major reviews have largely agreed that arrhythmias are more pronounced in patients with a coexisting cardiac risk factor such as existing QT-interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or arrhythmias, or who are on class IA and III antiarrhythmic drugs.[26–28]

Other potential adverse effects of long-term azithromycin treatment are gastrointestinal symptoms and hearing impairment.[29,30] A review of potential drug interactions is advised when patients are placed on long-term azithromycin therapy.

Although azithromycin is generally well tolerated, long-term treatment should be individualized and the benefits weighed against the risks. Patients should be monitored during treatment for any of the above adverse effects.

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