Expert recommendations on the role of macrolides in chronic respiratory diseases

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ABSTRACT

Background: India contributes to 32% of the total global disability-adjusted life years, due to chronic respiratory diseases. This has led to a high rate of health loss from these diseases. Antibiotics are commonly used in the management of respiratory disorders. With excellent tissue penetration, prolonged tissue persistence, and favorable side effect profile, macrolides are one of the best treatment options being recommended for respiratory, urogenital, dermal, and other bacterial infections. Still, there is a lack of clinical trial data on the use of macrolides in the management of respiratory chronic disease, and hence, there is a need for clinical guidance on their use in Indian setting. **Methods:** A systematic review of the literature was conducted on PubMed, Cochrane database, and Google Scholar. Existing guidelines, meta-analyses, systematic reviews, randomized controlled trials (RCTs), non-RCTs, landmark studies, and key-cited articles were selected. Recommendations were based on available evidence and expert panel's logical empiricism and consensus. **Results and Discussion:** This article discusses evidence-based and clinical practice based management of chronic respiratory conditions including chronic obstructive pulmonary disease, asthma, bronchiectasis, diffusive panbronchiolitis, and organizing pneumonia. The authors reviewed different respiratory conditions, role of macrolides in their management, adverse events and antimicrobial resistance associated with macrolides, evidence review of various clinical trials, guideline recommendations, and clinical recommendations.

KEY WORDS: Macrolides, chronic respiratory diseases, azithromycin, bronchiectasis, COPD, asthma

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INTRODUCTION

Chronic respiratory diseases comprise chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, and interstitial lung disease (ILD). Of these diseases, COPD and asthma are the most common, with COPD being the second most common cause of noncommunicable deaths globally and in India.[1]

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EPIDEMIOLOGY AND BURDEN OF CHRONIC RESPIRATORY DISORDERS

With a share of 18% of the total world population, India is witnessing an ever-increasing burden of chronic respiratory diseases. In a study conducted to estimate the prevalence of major chronic respiratory diseases, deaths, and disability-adjusted life years (DALYs) caused by them for every state of India from 1990 to 2016, it was seen that 10.9% of the total deaths and 6.4% of the total DALYs in India in 2016 were contributed by chronic respiratory diseases. India contributes to 32.0% of the total global DALYs due to chronic respiratory diseases.[1]

The number of cases of COPD in India increased from 28.1 million in 1990 to 55.3 million in 2016, which are reflected as a percentage increase in the prevalence from 3.3% to 4.2%. There were 37.9 million cases of asthma in India in 2016, with similar prevalence in the four epidemiological transition level (ETL) state groups; however, the highest DALY was in the low ETL state group. It is important to note that the DALYs per case of COPD and asthma were 1.7 and 2.4 times higher in India than the global average in 2016, respectively. Of the DALYs due to COPD in India in 2016, 53.7% were attributable to air pollution, 25.4% were attributable to tobacco use, and 16.5% were attributable to occupational risks, making these the leading risk factors for COPD.[1] Another study conducted in 2015 comprising 1560 pulmonologists, intensivists, and pediatricians also showed that almost 63% of the patients visited doctor's clinic due to chronic respiratory diseases, the most common of them being COPD, tuberculosis, asthma, and allergic rhinitis.[2]

The number of patients of bronchiectasis has also increased inexorably in the past decade, playing an important role in increasing burden on the global as well as Indian healthcare systems.[3]

It is clearly seen that India has an unduly large burden of chronic respiratory diseases. The increasing contribution of these diseases to the overall disease burden across India and the high rate of health loss from them clearly outline the need for established recommendations for clinical management of these conditions.[1]

ROLE OF MACROLIDE ANTIBIOTICS IN THE MANAGEMENT OF THE CHRONIC RESPIRATORY DISEASES

The treatment of airway disease is guided by the disease present and its severity.[4] Antibiotics are commonly employed for the management of respiratory disorders, such as cystic-fibrosis, bronchiectasis, asthma, and COPD. Oral antibiotics such as macrolides are widely used as antimicrobial agents due to their anti-inflammatory and prokinetic properties.[5]

Macrolides are also one of the best treatment options, owing to their excellent tissue penetration, prolonged tissue persistence, and favorable side effect profile when administered orally.[6] Along with their microbicidal properties, macrolides are also laced with immunomodulatory action and have the ability to suppress hyperimmunity and inflammation. The nonribosomal actions of macrolides consist of immunomodulation, decrease in bacterial virulence and biofilm formation, and reduction of mucus hypersecretion. These nonmicrobicidal actions of macrolides are manifested in a period of several weeks and are limited to the 14 and 15 member macrolides, such as erythromycin, clarithromycin, and azithromycin.[6]

Macrolides such as azithromycin are indicated for respiratory, urogenital, dermal, and other bacterial infections and exert immunomodulatory effects in chronic inflammatory disorders. Modulation of host immune responses is the reason behind its long-term therapeutic use in bronchiectasis, exacerbations of COPD, and non-eosinophilic asthma.[7]

METHODS

The current review assesses the recent evidence on chronic respiratory diseases and the role of macrolides in their treatment. The review presents evidence-based and clinical practice-based recommendations on the use of macrolides in the management of chronic respiratory diseases, including bronchiectasis, bronchiolitis, COPD, and asthma.

To impart the highest possible evidence base for the use of macrolides in the management of chronic respiratory diseases, a systematic review of the literature was conducted on PubMed, Cochrane database, and Google Scholar. Existing guidelines, meta-analyses, systematic reviews, randomized controlled trials (RCTs), non-RCT studies, and key-cited articles relating to the management of the conditions stated above were selected and reviewed. Only articles that were in English language and on chronic respiratory disorders, COPD, asthma, bronchiectasis, and bronchiolitis were included. Articles in other foreign language and focusing on other respiratory disorders were excluded from the selection.

Recommendations for each section were framed on the basis of available evidence. These were then discussed by the expert panel, and where there was little or no evidence, the panel relied on logical empiricism and consensus to generate the recommendations about the rational use of macrolides in chronic respiratory diseases.

RESULTS AND DISCUSSION

Chronic obstructive pulmonary disease

Chronic inflammation of the lung parenchyma and peripheral airways with an increase in alveolar

macrophages, neutrophils, T-cells (predominantly Th1-cells and Th-17-cells), and innate lymphoid cells is the hallmark feature of COPD. Even though most of the patients have neutrophilic inflammation, some also exhibit elevated eosinophil counts in the sputum.[8]

Standard therapies for COPD include bronchodilators and anti-inflammatory agents such as high-dose inhaled corticosteroids (ICS). A meta-analysis conducted in 2013 has shown that macrolide therapy significantly lowered the risk of acute exacerbations for COPD patients compared with no macrolide treatment. Subgroup analyses of the results showed that beneficial effects of macrolide therapy in reducing the exacerbation frequency of COPD were only seen with erythromycin therapy for 6 or more months. However, the immunoregulation effect was seen in erythromycin as well as other 14-and 15-membered ring macrolides, including clarithromycin, roxithromycin, and azithromycin. In addition, the study also showed that the use of macrolides led to a minor increase in the nonfatal adverse effects, such as gastrointestinal reactions, ototoxicity, rash, and liver injury. It was suggested that the incidence of these nonfatal adverse effects may be seen after therapy duration of at least 12 months.[9] Still, the optimal duration of macrolide therapy for COPD is not well established; however, available data suggest that significant benefits require no <6 months of treatment in COPD patients.[9] Four RCTs have compared a macrolide with placebo for preventing COPD exacerbation and have reported a significant reduction of exacerbations in the macrolide-treated group.[10] Another multicenter RCT comparing azithromycin in 250 mg daily dose with placebo for 12 months in 1142 patients with COPD considered at high risk for exacerbation showed that azithromycin not only delayed the time for the appearance of the first exacerbation but also reduced the rate of exacerbations.[10]

A study conducted in 2015 has shown that long-term macrolide therapy such as with azithromycin can reduce exacerbations of COPD.[11] Guidelines also recommend the use of long-term azithromycin in patients who are at risk of recurrent exacerbations.[11]

Ni *et al*. conducted a meta-analysis in 2015 and reported that macrolides possess a variety of immunomodulatory and physiological properties including anti-inflammatory and antiviral effects, reducing mucus secretions, and inhibiting bacterial virulence and biofilm formation.[12] Acute exacerbation of COPD is linked with an aggravation of inflammation and infections in the airway. Hence, prophylactic treatment with macrolides can bring about significant reduction in the rate of COPD exacerbations in patients.[13,14] The meta-analysis results indicated azithromycin therapy for 6–12 months to be effective.[12] A randomized trial was conducted to assess the use of azithromycin in reducing the frequency of exacerbations in patients who were at an increased risk of exacerbations but without any hearing impairment, resting tachycardia, or apparent risk of the corrected QT interval. The findings of the study showed that daily treatment with azithromycin for 1 year, given as an addition to the standard treatment, led to a significant reduction in the frequency of the exacerbations and improvement in the quality of life of the patients.[15]

The COLUMBUS trial was a randomized, double-blind, placebo-controlled, single-center trial conducted in the Netherlands between 2010 and 2014. The results of the trial showed that maintenance treatment with azithromycin was responsible for a significant reduction in the exacerbation frequency compared with placebo and hence should be considered for the use in patients with COPD who have frequent exacerbator phenotype and are refractory to standard care.[16] A retrospective observational study among severe COPD patients reported long-term reduction of exacerbation frequency when they were given azithromycin 250 mg at least 3 times in a week for 6 months. The benefits of azithromycin therapy were seen even after 1 year of treatment. The benefits of treatment outweigh the probable risks and adverse events involved in patients colonized with *Pseudomonas aeruginosa*.[17]

Guideline recommendations

The GOLD guidelines 2019 recommend that the long-term use of azithromycin and erythromycin therapy reduces exacerbations over 1 year. However, it should also be noted that treatment with azithromycin is associated with an increased incidence of bacterial resistance.[18]

Expert recommendations

1. Macrolide antibiotic is recommended to be used in COPD patients with frequent exacerbations (≥3 per year), patients with coexisting bronchiectasis, disease of older patients by definition patients, and those with stable neutrophilic bronchitis
2. The recommended dose is erythromycin 500 mg BD or azithromycin 250 mg OD or 500 mg thrice a week, with preferred therapy being azithromycin 250 mg thrice weekly or 500 mg thrice a week
3. Treatment duration: Greater than 6 months; preferably 6–12 months
4. The patients are recommended to abstain from smoking during the therapy for better benefits
5. Recommendations for good clinical practice are frequent audiometry for the assessment of hearing impairment and electrocardiogram (ECG) for QT interval.

Asthma

Chronic airway inflammation, reversible airway obstruction, and airway hyper-responsiveness are the characteristic features of asthma. In eosinophilic asthma, eosinophils, mast cells, and Th2-mediated inflammation play a prominent role in the disease manifestation. In severe case, neutrophils and interleukin-8 (IL-8) concentrations are also increased in the airway.[8]

The results of a study conducted among a group of 11 patients with mild asthma suggested that

8 weeks of intermittent, low-dose administration of azithromycin might reduce the severity of bronchial hyper-responsiveness.[19] Another study on 16 asthmatic children treated with azithromycin exhibited that a short course of azithromycin is associated with the elimination of bronchial hyper-responsiveness and reduction in airway neutrophil infiltration in some children with asthma.[20] Existing evidence suggests that the use of macrolides such as azithromycin and erythromycin exhibit improved efficacy in patients with suboptimally controlled severe neutrophilic asthma and with asthma exacerbations.[21] The AZISAST trial showed that even though azithromycin did not reduce the rate of severe exacerbations in patients with severe asthma, still there was a significant reduction in the rate of severe exacerbations in azithromycin-treated patients with noneosinophilic severe asthma. Severe asthma was defined as asthma which is heterogeneous, encompassing eosinophilic and noneosinophilic (mainly neutrophilic) phenotypes.[22] A 2013 meta-analysis of 12 RCTs of macrolides for the long-term treatment of asthma in both adults and children found positive effects on improving pulmonary function, asthma symptoms, asthma quality of life, and airway hyper-responsiveness.[23,24] The updated 2015 Cochrane review of 18 RCTs reported positive benefits on asthma symptoms.[25]

A randomized, double-blind, placebo-controlled trial in children showed that azithromycin reduced the duration of episodes of asthma-like symptoms in young children. The results suggest that azithromycin may have a role in acute management of exacerbations.[26]

The AMAZES trial, a randomized, double-blind, placebo-controlled, parallel-group trial, conducted to assess the efficacy of oral azithromycin in asthma, showed that it significantly improved the quality of life of patients. The trial results showed that after treatment with oral azithromycin for 48 weeks, adults with persistent symptomatic asthma show fewer asthma exacerbations and improved quality of life. The study suggests that azithromycin may be a useful add-on therapy in persistent asthma. In this trial, it was seen that azithromycin reduced exacerbations in all phenotypes of patient – namely eosinophilic and noneosinophilic.[27] It has been evident that adults with uncontrolled persistent asthma require additional therapy in spite of being on long-term maintenance therapy. Evidence from AZISAST and AMAZES trials has shown that the use of azithromycin as an add-on treatment (three times a week) for adult patients with persistent symptomatic asthma, despite moderate–high-dose ICS and long-acting beta$_2$ agonists (LABA), reduced asthma exacerbations in eosinophilic and noneosinophilic asthma as well as improved quality of life in asthma patients.[22,27]

Guideline recommendations

A joint European Respiratory Society/American Thoracic Society guideline on severe asthma recommends against the use of macrolides in the management of asthma. However, the Global Initiative for Asthma (GINA) 2019 guidelines recommends the use of low-dose azithromycin as an add-on treatment for patients with symptomatic asthma despite moderate–high-dose inhaled corticosteroid-long acting beta2 agonists (ICS-LABA). GINA guidelines (2019 update) recommended to consider, "add-on azithromycin (three times a week, off label), for adult patients with persistent symptomatic asthma despite moderate–high-dose ICS and LABA, reduced asthma exacerbations in eosinophilic and noneosinophilic asthma and improved asthma-related quality of life." As per the guidelines, add-on low-dose macrolide may be considered if there is no evidence of type 2 inflammation in patients; if the patient has not had a good response to any type 2 targeted therapy. The guideline also cautions that before considering add-on off-label therapy with azithromycin in adult patients with uncontrolled or severe asthma, sputum should be assessed for atypical mycobacteria, and the risk of increase in antimicrobial resistance (AMR), both at patient and population level, should be considered.[28]

Expert recommendations

1. The use of azithromycin can be considered in certain subsets of patients with poor control of asthma despite receiving ICS/LABA/LAMA
2. Treatment decisions should be individualized taking into account possible benefits and risks of adverse effects and the possibility of increased macrolide resistance
3. It is recommended that the potential for adverse effects should be carefully considered in such conditions
4. Before initiating add-on therapy with azithromycin in adult patients with uncontrolled or severe asthma, sputum should be checked for atypical mycobacteria and the risk of antimicrobial resistance should also be considered
5. Recommendations for good clinical practice are frequent audiometry for assessment of hearing impairment and ECG for QT interval
6. Antibiotics are not recommended in asthma exacerbations unless there is strong evidence of bacterial lung infections. In case of an infective exacerbation, a beta-lactam-like co-amoxiclav or quinolone-like levofloxacin is recommended. Low-dose macrolide and quinolone should not be given simultaneously.

Bronchiectasis

Bronchiectasis is characterized by permanent enlargement of the bronchi.[8] It is clinically manifested as cough, sputum production, and recurrent respiratory infections.[29] The choice of the antibiotic is based on the causative organisms and sensitivities.[30]

A series of pivotal studies offers strong evidence in favor of low-dose macrolide therapy for the reduction of the frequency of exacerbations in patients with bronchiectasis. The BLESS RCT showed that long-term, low-dose erythromycin caused a significant reduction in the frequency of pulmonary exacerbation and also

decreased 24-h sputum production and lung function decline.[31] The EMBRACE study showed that azithromycin was associated with 62% reduction in exacerbation rates compared with placebo, but no significant changes in pulmonary function.[32] The BAT study also showed that the use of azithromycin is associated with a reduction in the time to first exacerbation and the number of patients experiencing exacerbations. It also caused an improvement in the quality of life as well as lung function.[33,34] Based on the results of these RCTs, it can be easily concluded that macrolides can be efficiently used for the treatment of bronchiectasis in both children and adult.[3]

A meta-analysis conducted in 2019 suggested that based on the existing evidence, macrolides and azithromycin, in particular, may be the most efficient treatment intervention in the management of bronchiectasis.[35] In a study to assess the efficacy of roxithromycin on airway inflammation and remodeling in patients with noncystic fibrosis bronchiectasis (NCFB) under steady state, it was observed that the use of roxithromycin can reduce airway inflammation and airway thickness of dilated bronchus in patients with NCFB.[36]

A double-blind, parallel-group study investigating the effect of 7-day treatment with clarithromycin, amoxicillin, and/or cefaclor showed that the short-term administration of the 14-membered macrolide reduced chronic airway hypersecretion in a significant number of patients.[37]

Guideline recommendation

The European Respiratory Society guidelines for the management of adult bronchiectasis recommend treatment with 14 days of antibiotic for acute exacerbations of bronchiectasis. In the European guidelines, the recommending task panel suggested that patients with mild exacerbations (those affected with pathogens more sensitive to antibiotics) may be benefitted by short-term antibiotic treatment. Long-term antibiotic treatments (≥3 months) for adults with bronchiectasis who have three or more exacerbations per year is also recommended. Long-term treatment with macrolides such as azithromycin and erythromycin is suggested for adults with bronchiectasis and chronic *P. aeruginosa* infection in whom an inhaled antibiotic is contraindicated, not tolerated, or feasible. Guidelines also suggest long-term treatments with macrolides (azithromycin and erythromycin) in addition to or instead of an inhaled antibiotic, for adults with bronchiectasis and chronic *P. aeruginosa* infection, who have a high exacerbation frequency, despite taking an inhaled antibiotic and in adults with bronchiectasis not infected with *P. aeruginosa*.[38]

The British Thoracic Society Guideline for bronchiectasis in adults, 2019 recommended long-term antibiotics in patients with bronchiectasis who experience 3 or more exacerbations per year. If the patient is colonized with *P. aeruginosa*, azithromycin or erythromycin is suggested to be used as an alternative or as an additive treatment to an inhaled antibiotic. If the patient is not colonized with *P. aeruginosa*, azithromycin or erythromycin forms the first line of treatment.[39]

Expert recommendation

1. Long-term antibiotic is recommended for patients with exacerbation frequency ≥3. Macrolides are recommended as the first line of treatment for patients with non-*Pseudomonas* bacteria
2. Azithromycin is a preferred choice of treatment in a dose of 250 mg once daily. 500 mg azithromycin thrice weekly or 250 mg thrice weekly may also be used for better patient compliance
3. Optimum duration of therapy: 3–6 months
4. Recommendations for good clinical practice: ECG should be monitored for QT prolongation, audiometry for hearing impairment detection
5. Azithromycin is best suited for sputum-producing patients
6. The first-line therapy in case of *Pseudomonas* infection is inhalation antibiotics such as tobramycin or colistin.

Bronchiolitis

Bronchiolitis is a chronic distal airway inflammation featured by diffuse micronodular pulmonary lesions generally consisting of neutrophils. Neutrophils and epithelial cells produce IL-8, which attracts more neutrophils.[8]

Long-term macrolide therapy has shown beneficial effect in diffuse panbronchiolitis (DPB).[6] Retrospective studies in patients who were receiving azithromycin 500 mg, 3 times a week showed similar results with erythromycin treatment and improved symptoms, better functioning of the lungs, improved arterial partial pressure of oxygen, as well as improved radiologic findings. The current recommendation for azithromycin is as the mainstay of treatment of DPB.[40] However, it is important to mention here that in India, bronchiolitis obliterans is more common, in which macrolides have no proven role.

A study conducted by Yamamoto *et al*. on 101 patients showed that DPB led to a significant improvement in dyspnea on exertion and sputum production in patients treated with erythromycin. An RCT was conducted by Tamaoki *et al*. and reported that macrolide in patients with DPB resulted in a change in sputum production. Another retrospective study showed that a significant improvement in survival resulted from long-term, low-dose erythromycin treatment.[41]

In a study conducted on 51 patients with DPB reported that the disease was completely cured with azithromycin therapy in 14 patients while symptoms were eliminated to some degree in 36 patients. It was effective and well tolerated for patients with DPB.[42]

A retrospective study conducted on 29 patients showed that azithromycin therapy for 6 months resulted in rapid improvement in lung function.[43]

Guideline recommendations

The clinical guidelines from the European Respiratory Society recommend the use of macrolides (erythromycin) 400 or 600 mg orally as the first choice of treatment in DPB. The second line of treatment is clarithromycin 200 or 400 mg orally or roxithromycin 150 or 300 mg orally.[44]

Expert recommendations

1. Systemic steroids with or without macrolides are recommended for 1–2 years. Azithromycin is given in a dose of 250 mg/day
2. Macrolides have no proven role in bronchiolitis obliterans which is commonly observed in India.

Table 1 enumerates the dosage regimen of azithromycin in different chronic lung diseases based on the clinical recommendations as well as guideline recommendations.

Safety and tolerability associated with macrolide use in chronic respiratory disorders

Recent research has suggested that patients treated with long-term macrolides could be at risk of increased infection with nontuberculous mycobacteria. In addition, long-term macrolide therapy may also be associated with underlying severe side effects, such as increased gastrointestinal disorders, cardiovascular events, and hearing impairment.[45]

A Cochrane review published in 2019, including 183 randomized placebo-controlled trials and involving 252,886 patients, suggested that the most commonly reported adverse events due to the macrolide antibiotics (azithromycin, erythromycin, clarithromycin, and roxithromycin) were gastrointestinal. It was reported that patients taking macrolide antibiotics experienced vomiting, nausea, diarrhea, abdominal pain, and gastrointestinal disorders (not otherwise specified) more frequently than those on placebo. Low-quality evidence also suggested that macrolides may be responsible for causing taste disturbances.[46]

A retrospective cohort study demonstrated that during 5 days of azithromycin therapy, a small absolute increase in cardiovascular deaths was observed.[47] In another study, it has been reported that the large majority of patients experiencing cardiac arrhythmias from macrolides had coexisting risk factors, and in the absence of coexisting risk factors, the incidence of arrhythmias was very low (less than one in 100,000 patients).[11] The 2019 meta-analysis has also suggested that there was no evidence pointing to the fact that macrolide use caused more cardiac disorder, hepatobiliary disorders, or alterations in liver enzymes as compared to placebo. Macrolides were not responsible for any increase in deaths in patients treated with macrolides compared to placebo.[46] Another meta-analysis reported that in a population at high risk for arrhythmias and other cardiac-associated adverse events, the risk of cardiac events related to macrolides is dependent on the extent to which adjustments are made for comorbidities and patient's demographical characteristics. One of the most used macrolides, i.e., azithromycin, has shown considerably smaller and statistically insignificant effects on cardiac events among high-risk patients.[48]

Another side effect of macrolide use is hearing decrement.[49] Results of AZISAST trial showed that azithromycin given to patients with severe noneosinophilic asthma improved quality of life of patients and was well tolerated. The long-term treatment with azithromycin was seen to be safe, with no difference in the frequency and severity of adverse events as compared to placebo. The study also suggested that when azithromycin was given to patients with eosinophilic severe asthma, a trend toward an increased rate of primary end points (severe asthma exacerbations and/or lower respiratory tract infections requiring antibiotics) was observed. The study did not report any patients with hearing loss, which is in contrast with hearing decrements observed in azithromycin-treated COPD patients.[22] In a meta-analysis, The use of azithromycin in bronchiectasis patients was associated with increased diarrhea and bacterial resistance.[50,51] The 2019 Cochrane review reported that when compared with study participants taking placebo, the participants taking macrolides experienced hearing loss more often; however, only four studies reported this outcome.[46]

We recommend a careful review of patient-level risk factors for ventricular arrhythmias before starting them on azithromycin. Smaller doses of azithromycin are recommended to be used in COPD patients.

Table 1: Expert recommendations and guideline recommendations for the dosage regimen of azithromycin in chronic lung diseases

Chronic respiratory disease	Expert recommendation		Guideline recommendation	
	Dose	Duration	Dose	Duration
COPD	250 mg OD or 500 mg thrice a week or 250 mg thrice weekly	6-12 months	250 mg/day or 500 mg three times per week	1 year
Asthma	250 mg per day for 5 days followed by 250 mg three times a week	6-12 months	Low dose azithromycin as an add-on treatment for patients with symptomatic asthma despite moderate–high-dose ICS-LABA; three times a week, off-label	
Bronchiectasis	250 mg once daily; 500 mg/thrice a week or 250 mg thrice weekly	3-6 months		≥3 months
Diffuse pan bronchiolitis	250 mg/day	1-2 years	400 or 600 mg orally	

COPD: Chronic obstructive pulmonary disease, ICS-LABA: Inhaled corticosteroid–long-acting beta2 agonists

Issues of antimicrobial resistance

In a meta-analysis including RCTs of azithromycin use in patients with chronic lung diseases, it was suggested that the long-term use of azithromycin (i) may lead to increased bacterial resistance in isolates from treated patients and (ii) may decrease colonization of bacteria and antibiotic use to some extent. A study showed that patients with bronchiectasis who use azithromycin were at risk of higher macrolide resistance than those with less exposure. It also suggested that azithromycin use was correlated with significantly reduced carriage of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*; however, it increased the carriage of *S. aureus* and macrolide-resistant strains of *S. pneumoniae* and *S. aureus* in a cumulative, dose-dependent manner.[45]

It is also feared that the widespread use of maintenance therapy with macrolides in COPD patients may result in microbial resistance in community populations; however, there has been no evidence indicating the spread of drug-resistant bacteria in the community.[50] The results of COLUMBUS trial showed that the decrease in frequency of acute exacerbations of COPD was accompanied by not only a decrease in the incidence of colonization with selected respiratory pathogens but also an increase in the incidence of colonization with macrolide-resistant organisms. However, there was no evidence to show that colonization increased the incidence of acute exacerbations of COPD or pneumonia. It is important to note that the COLUMBUS trial only offers safety profile of azithromycin when it is taken for 1 year and does not give any information, regarding the potential adverse effects of long-term macrolide administration on bacterial resistance patterns in the community.[15]

A study showed that short-term treatment with macrolides induced a significant increase in macrolide-resistant pharyngeal streptococci in healthy volunteers.[52] The AZISAST trial showed that long-term treatment with azithromycin led to an increased proportion of macrolide-resistant oropharyngeal streptococci,[22] which was in sync with the COPD Clinical Research Network study showing an increased incidence of macrolide resistance in the nasopharyngeal flora.[15] However, none of these studies provided evidence that colonization with macrolide-resistant organisms increased the risk of lower respiratory tract infections or pneumonia.[22] In a study where patients with bronchiectasis were treated with azithromycin, a significant reduction in frequency of acute exacerbations was seen with an increase in the isolation of bacterial strains resistant to azithromycin in the nasal swab samples from the study group.[53] In a review, an increase in oropharyngeal carriage of macrolide-resistant commensals was reported which is usually harmless, but can cause infection in immunocompromised hosts, or transfer the resistance acquired by the pathogens.[54] In spite of the fact that the long-term use of azithromycin induces nasopharyngeal and oropharyngeal flora in patients, the long-term effects of macrolide treatment on microbial resistance in the community are unknown.

In another review of the available evidence, an increased risk of the development of macrolide-resistant *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *H. influenzae* related to long-term macrolide use was reported. In spite of this, there has been no evidence to suggest negative consequences, such as increased exacerbations, increased use of IV antibiotics, or increased hospitalizations. However, it is important to mention here that long-term studies are needed to detect these types of outcomes, resulting from antimicrobial resistance.[33]

The 2019 Cochrane review published in 2019 also suggested that the macrolide-resistant bacteria were more commonly identified in patients immediately after exposure to the antibiotic; however, the difference in the resistance at later stages was always found to be inconsistent.[46] Hence, it is recommended that long-term use of macrolides such as azithromycin for patients with chronic lung diseases should be considered carefully.

CONCLUSION

The prevalence of chronic respiratory diseases is ever increasing in India, with COPD and asthma being the most prevalent. The treatment of the respiratory disease is determined by the type and the severity of the disease. Oral antibiotics such as macrolides are widely used as antimicrobial agents as well as for their immunomodulatory action. Macrolides such as azithromycin are recommended for use in various conditions including COPD, asthma, bronchiectasis, and DPB. Long-term use of azithromycin in patients with chronic respiratory diseases is also linked with cardiovascular and otological toxicities and the emergence of resistant bacteria. The macrolide antibiotics have been clearly reported to increase the rate of gastrointestinal adverse events such as nausea, vomiting, abdominal pain, and diarrhea. However, there is no evidence suggesting that macrolides cause more cardiac disorders, liver disorders, or blood infections. Macrolides are widely used as the first line therapy of respiratory infections, but there is a concern that their long-term use may promote antimicrobial resistance. It has also been suggested that widespread use of macrolides such as azithromycin can have significant effect on antimicrobial resistance rates of several microbial agents. While advising azithromycin, patients should be screened carefully for cardiovascular risk factors and atypical bacteria in the sputum. Even though data from RCTs and retrospective studies are available, there is a pressing need for trial data on azithromycin on Indian population for a better guidance on the drug regimen and its use in various conditions.

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