Role of Clarithromycin in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Agam Vora

Abstract
The prevalence of chronic obstructive pulmonary disease (COPD) is increasing in under-developing and developing countries. As per current estimations, COPD will become the third leading cause of death globally, by 2030. Long-acting anti-cholinergic agents, β2-agonists, inhaled corticosteroids, antibiotics and mucolytics are few of the agents currently used in the treatment of COPD, which improve the symptoms and overall quality of life. Several of the important classes of antibiotics are used in the management of COPD including penicillins, cephalosporins, tetracyclines, fluoroquinolones, sulphonamides, aminoglycosides and macrolides. Macrolide antibiotics such as erythromycin, clarithromycin and azithromycin have a variety of physiological activities other than their antimicrobial effects, ultimately helping in preventing exacerbations and reducing mortality rates. Clinical studies indicate that long term use of clarithromycin is effective in the treatment of COPD exacerbations with lower incidence of adverse effects. This descriptive review on the role of the clarithromycin in treatment of COPD exacerbations will highlight these properties of clarithromycin in detail.

COPD Exacerbations
The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define an exacerbation as ‘an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.’ Generally, COPD is classified into three types; type I, type II and type III (Table 1).3

The COPD exacerbations are caused by a variety of risk factors such as environmental irritants, heart failure or medication noncompliance. However, most often, exacerbations are the outcome of bacterial or viral infections (Table 2).4

Management of COPD Exacerbations
Clinically, COPD exacerbations are described by enhanced airway inflammation, oedema and systemic inflammation. The morbidity and mortality caused by exacerbations can be minimized with early treatment initiation. The ‘ABC approach’, the pharmacological treatment approach for COPD exacerbations, is an acronym which reflects the three classes of drugs i.e antibiotics, bronchodilators and corticosteroids (Tables 3 and 4).5

Background
The increasing prevalence of chronic obstructive pulmonary disease (COPD) is a major concern in under-developing and developing countries, as these countries contribute to almost 90% of COPD deaths. As per current estimates, COPD will become the third leading cause of death globally, by 2030. Although the prevalence of COPD is not well-established presently in India, a series of researches performed by some scientists have suggested that it may be around 5% in the adult population, with higher prevalence reported in smokers, men and subjects from rural area, depending on the socio-economic status, use of domestic fuel (type) etc.1

Long-acting anti-cholinergic agents, β2-agonists, inhaled corticosteroids, antibiotics and mucolytics are some of the agents currently used in the treatment of COPD, to improve symptoms and overall quality of life. Macrolide antibiotics such as erythromycin, clarithromycin and azithromycin have a variety of physiological activities other than their antimicrobial effects, eventually helping in preventing exacerbations and reducing mortality rates.2 Clarithromycin, a macrolide antibiotic, has been found to be effective in treatment of COPD exacerbations due to its antibacterial and immune modulator properties.
Management of COPD

Antibiotics in the Viruses

Table 1: Classification of acute exacerbations of COPD (AECOPD)

<table>
<thead>
<tr>
<th>Type I (most severe)</th>
<th>Type II</th>
<th>Type III</th>
</tr>
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<tbody>
<tr>
<td>Severe exacerbations</td>
<td>Any two symptoms present</td>
<td>One symptom present plus at least one of the following:</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Pseudomonas species</td>
<td>• An upper respiratory tract infection in the past 5 days</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Other gram-negative enteric bacilli</td>
<td>• Increased wheezing</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td></td>
<td>• Increased cough</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td></td>
<td>• Fever without an obvious source</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
<td>• A 20% increase in respiratory rate</td>
</tr>
<tr>
<td>Viruses</td>
<td></td>
<td>• Heart rate above baseline</td>
</tr>
</tbody>
</table>

Table 2: Most common infectious causes of COPD exacerbations

<table>
<thead>
<tr>
<th>Mild to moderate exacerbations</th>
<th>Severe exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Pseudomonas species</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Other gram-negative enteric bacilli</td>
</tr>
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<td>Moraxella catarrhalis</td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
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</table>

Antibiotics in the Management of COPD Exacerbations

The concentration of bacteria is high in lower airways in patients with COPD exacerbations. Antibiotics have a significant effect on peak expiratory flow rate (PEFR) and cause an earlier resolution of all three of the cardinal symptoms, viz: increased dyspnoea, increased sputum volume and increased sputum purulence. A study performed to evaluate the relationship between sputum purulence and the presence of bacteria suggested that patients should be treated with antibiotics if they also have at least one of the other two symptoms (dyspnoea or increased sputum volume) along with sputum purulence.5

As antibiotic therapies have shown positive effects on clinical recovery and treatment outcome in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), the use of antibiotics is recommended from the initial treatment stage itself. Regular use of antibiotics may reduce severity and duration of AECOPD episodes.4

Further, the mortality and incidence of secondary nosocomial pneumonia may increase, if COPD exacerbations are not treated with antibiotics. It is recommended that antibiotic selection should be focused against Streptococcus pneumoniae, Moraxella catarrhalis and Haemophilus influenzae. Further, the Pseudomonas aeruginosa infection should be treated with broader antibiotic exposure.7 Some classes of antibiotics used in the management of COPD includes penicillins, cephalosporins, tetracyclines, fluoroquinolones, sulphonamides, aminoglycosides and macrolides. The commonly used antibiotics are elucidated in Table 5.4

Orally administered doxycycline, trimethoprim-sulfamethoxazole or amoxicillin-clavulanate potassium are usually considered in the initial outpatient management. It is recommended that hospitalized patients should get intravenous treatment with an antipseudomonal penicillin, a third-generation cephalosporin, a newer macrolide or a fluoroquinolone, depending on local bacterial resistance patterns.4 Penicillin corresponds to a group of beta (β)-lactam antibiotics. Hypersensitivity reaction is major problem in the use of penicillin. If a patient has symptoms of allergic reactions, re-exposure to penicillin can trigger life-threatening anaphylaxis. It has been estimated that up to 60% of penicillin-allergic patients will experience another allergic incident if dose of the drug is repeated.8

Amoxicillin–clavulanic acid combination is available in a range of doses like 250/125 mg (2:1), 500/125 mg (4:1), 875/125 mg (7:1), 1000/125 mg (8:1), and 2000/125 mg (16:1). However, insufficient doses and inappropriate use of the combination may result in drug resistance.9 Although, previously conducted trials such as TACTIC (Acute Exacerbations of Chronic Bronchitis), GLOBE (Gemifloxacin Long-term Outcomes in Bronchitis Exacerbations) and MOSAIC (Moxifloxacin to Standard oral antibiotic regimen) have revealed better results with newer generation fluoroquinolones as a first line

Table 3: Advantages and disadvantages of pharmacological treatment

<table>
<thead>
<tr>
<th>Bronchodilators</th>
<th>Systemic corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve symptoms and forced expiratory volume-one second (FEV1)</td>
<td>Improve symptoms, FEV1, and PaO2 in moderate to severe exacerbations</td>
</tr>
<tr>
<td>No differences between different classes</td>
<td>Reduce treatment failure, relapse and length of hospital stay</td>
</tr>
<tr>
<td>No differences between metered-dose inhaler (MDI) and nebulizer use</td>
<td>Induce more side effects (such as hyperglycaemia)</td>
</tr>
<tr>
<td>Discrete effects on symptoms and lung function</td>
<td>Numerous side effects</td>
</tr>
<tr>
<td>Oral route is preferred and cheaper</td>
<td></td>
</tr>
<tr>
<td>Unlikely benefit of short courses of antibiotics in most patients</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: GOLD 2017 recommendations for antibiotics use

COPD exacerbation rates may be reduced with the regular use of macrolide antibiotics. Antibiotics when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure and hospitalization duration. (Duration of therapy should be 5-7 days).

Antibiotics should be given to patients with exacerbations of COPD:

- Who have three cardinal symptoms, i.e.: increase in dyspnoea, sputum volume and sputum purulence
- Have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms
- Require mechanical ventilation (invasive or non-invasive)
Table 5: Commonly used antibiotics for treatment of COPD exacerbations*

Mild to moderate exacerbations*

**Macrolides**
- Clarithromycin, 500 mg twice daily
- Azithromycin, 500 mg initially, then 250 mg daily

**Amoxicillin-clavulanate potassium**
- 500 mg/125 mg tablet three times daily
- 875 mg/125 mg tablet twice daily

**Fluoroquinolones**
- Levofloxacin, 500 mg daily
- Gatifloxacin, 400 mg daily
- Moxifloxacin, 400 mg daily
- Doxycycline (100 mg twice daily)
- Trimethoprim-sulfamethoxazole (one tablet twice daily)

Moderate to severe exacerbations**

**Cephalosporins**
- Ceftriaxone, 1 to 2 g IV daily
- Cefotaxime, 1 g IV every 8 to 12 hours
- Cefazidime, 1 to 2 g IV every 8 to 12 hours

**Antipseudomonal penicillins**
- Piperacillin-tazobactam, 3.375 g IV every 6 hours
- Ticarcillin-clavulanate potassium, 3.1 g IV every 4 to 6 hours

**Fluoroquinolones**
- Levofloxacin, 500 mg IV daily
- Gatifloxacin, 400 mg IV daily

**Aminoglycoside**
- Tobramycin, 1 mg per kg IV every 8 to 12 hours, or 5 mg per kg IV daily

IV: Intravenous; * For orally administered antibiotics, the usual duration of therapy is five to 10 days; ** Drugs are often used in combination for synergy; IV therapy is usually employed

therapy, guidelines recommend that fluoroquinolones should be reserved for treatment failures and those with risk factors for poor outcome.

The use of amoxicillin, doxycycline or cotrimoxazole is recommended as a first line agent if the risk factors for poor outcome (comorbid illness, severe COPD, frequent i.e. >3 years’ exacerbations) and the antimicrobial use in the last 6 months is absent. Antibiotics like cefuroxime axetil, amoxyccillin-clavulonic acid, and macrolides such as azithromycin clarithromycin are suggested in case of failure of first line agents. Macrolides have excellent tissue penetration and antimicrobial activity, mainly against gram-positive cocci and atypical pathogens. The varied biological activities and ability to modify inflammation has led to their use in the treatment of asthma, bronchiectasis and COPD.

**Macrolide antibiotics**

Macrolides usually have macrocyclic lactone ring of 12 or more elements. They comprise of bioactive agents, antibiotics, antifungal drugs, prokinetics, and immunosuppressants. The widely used antibiotics family of drugs are 14-, 15-, and 16-membered macrolides. The first macrolide antibiotic, erythromycin, was used in the treatment of upper respiratory tract, skin and soft tissue infections previously, in patients who are allergic to penicillin. However, numerous adverse effects such as frequent gastrointestinal intolerance and short serum half-life have limited the use of erythromycin.

The macrolides, azithromycin, clarithromycin, roxithromycin, ketolide and telithromycin, are the advanced structural analogues of erythromycin. They exhibit broader activity, more favourable pharmacokinetics and pharmacodynamics, and better tolerability when compared to erythromycin. Clarithromycin and azithromycin are widely used in the management of respiratory tract infections. Evidences have shown that the long term treatment with azithromycin and clarithromycin in patients with COPD is effective and tolerable, with subsequent decrease in exacerbations and associated hospitalizations.

Further, the studies have confirmed that the effects of clarithromycin and roxithromycin in the inhibition of inflammatory cytokine production by COPD sputum cells were more effective than that of azithromycin. However, clarithromycin exhibited less adverse events in the treatment of respiratory tract infections when compared to roxithromycin.

**Role of Clarithromycin in COPD Exacerbations**

Clarithromycin, 6-O-methylerythromycin, is produced when C-6 hydroxy(-OH) group of erythromycin is replaced with methoxy (-CH3) group. This substitution results into a more acid stable antimicrobial agent which inhibits the degradation of erythromycin base to the hemiketal intermediate. The improvement in oral bioavailability and reduction in gastrointestinal intolerance was observed in clarithromycin due to increased acid stability.

The 14-hydroxylclarithromycin is an active metabolite of clarithromycin. Higher doses of clarithromycin results in nonlinear increase in the serum half-life and in the area under the plasma concentration curve (AUC) of clarithromycin. Administration of 500 mg clarithromycin (every 8 to 12 hours) resulted in a steady state peak plasma concentrations of 3 to 4 mg/L within 3 days, with elimination half-life increasing up to 5 to 7 hours.

**Mechanism: Clarithromycin mediated prevention of COPD exacerbation**

**Anti-inflammatory effect**

Macrolides suppress mRNA levels and release of IL-8 by activating nuclear factor-kB and activator protein-1. Studies have reported that macrolide mediates anti-inflammatory effects in the sputum of patients with COPD, resulting in decreased total cell counts, neutrophil chemotaxis and IL-8 and tumour necrosis factor (TNF)-α levels. Clarithromycin reduces the release of viruses and cytokines into supernatant fluids in humans infected with seasonal type A influenza. Anti-inflammatory effects of macrolides may be associated with the inhibition of viral infection induced COPD exacerbations.
**Antibiotic effect**

Clarithromycin reduces the production of pneumolysin, a vital virulence factor in the infection of *S. pneumoniae*. It also inhibits the twitching motility of *P. aeruginosa* and alters the structure and architecture of the biofilm. The production of pro-inflammatory cytokines, soluble intercellular adhesion molecule (ICAM)-1 and mucin is decreased by macrolides in cells such as airway epithelial cells, in response to endotoxin and extract of *H. influenzae.*

**Immunomodulatory effect**

The long term treatment with clarithromycin decreases sputum production and volume in patients. A study conducted in rats reported that clarithromycin inhibited ovalbumin (OVA)-and lipopolysaccharide (LPS)-induced mucus production activated by the intranasal instillation of OVA in OVA-sensitised rats and intranasal LPS instillation. Some of the *in vitro* studies also showed that clarithromycin inhibits mucin or MUC5AC production or secretion after stimulation with TNF-α, RV infection or extract of *H. influenzae* in airway epithelial cells.

The preclinical study performed in mice infected with a lethal dose of influenza virus suggested that clarithromycin increases the survival rate. The study also reported that clarithromycin induced mechanisms such as the reduced production of nitric oxide, reactive oxygen species and interferon (IFN)-γ; elevated IL-12 levels are associated with the reduction in lung injury and the severity of pneumonia.

**Clinical evidences**

The use of clarithromycin in acute exacerbation of COPD had been studied in a few clinical trials. Shmelev EI *et al.* studied the effect of clarithromycin in the treatment of moderate and severe exacerbations of stage II COPD. The study compared clinical efficacy of clarithromycin with beta-lactams and respiratory fluoroquinolones. The results from the study suggested that clarithromycin has equal clinical efficacy and minor side effects when compared with the controlled drugs. Thus, study concluded that clarithromycin can be used as the initial therapy for exacerbations of COPD in a daily practice.

Léophonte and colleagues performed study to evaluate the effect of routine use of clarithromycin tablet in the treatment of acute exacerbations of non-severe COPD. It was an open label, pharmacoepidemiological, clinical study in community practice which was performed with 180 practitioners. Seven hundred and nineteen adult patients with acute exacerbation of mild or moderately severe COPD participated in the study. About 92.5% of subjects showed a favourable clinical course of exacerbations and 99% of cases showed resolution of frankly purulent sputum, which was associated with good tolerance. The study confirmed the use of clarithromycin as a first line therapy in bacterial exacerbation of mild or moderately severe, stable COPD.

Basyigit I *et al.* evaluated the anti-inflammatory effect of clarithromycin on serum and sputum interleukin-8 (IL-8), tumour necrosis factor-α (TNF-α), and leukotriene B4 levels in patients with COPD. It was a prospective, single-center, double-blind, placebo-controlled study which included thirty men with mild to moderate COPD. Patients received either clarithromycin or placebo for 14 days. The levels of IL-8, TNF-α and the induced sputum total cell counts decreased significantly in the clarithromycin group post-treatment compared to the pre-treatment levels (Figure 1). Likewise, significant decrease in levels of serum inflammatory markers was observed in the clarithromycin group compared to placebo group. The study suggested that the reduction in the levels of IL-8 and TNF-α might be related to the anti-inflammatory effect of clarithromycin. Thus, clarithromycin can be used to treat infection or help control the inflammation in patients with COPD.

Banerjee D *et al.* studied the effect of oral clarithromycin on bronchial airway inflammation in moderate to severe stable COPD. It was a prospective, double blind, controlled trial in patients with moderate to severe stable COPD. Patients received therapy with oral modified-release clarithromycin 500 mg/day or placebo for 3 months. Thirty-one patients were treated with clarithromycin and thirty-six with placebo, out of total 67 patients. Although, clarithromycin had insignificant effect on sputum total cell count, neutrophil count, IL-8, Leukotriene B4, TNF-α levels or neutrophil elastase, it did cause a small reduction in the neutrophil differential (p = 0.04 relative to placebo) and neutrophil chemotaxis (p = 0.058 relative to placebo).

**Safety profile of clarithromycin**

The safety profile of clarithromycin has been well documented. Clarithromycin is well-tolerated in most of the studies. A research study conducted in COPD patients suggested that gastrointestinal intolerability and taste perversion are common side effects with clarithromycin therapy. The other common adverse reactions (nausea [3.8%], diarrhoea [3%], abdominal pain [1.9%], and headache [1.7%]) reported with clarithromycin are similar to other macrolides. Overall, the results from the studies suggested that fewer than 3% of patients receiving clarithromycin withdrew from studies because of adverse effects. Laboratory abnormalities which included abnormal liver function tests and decreased white blood cell counts were also rare.
Place in Therapy

COPD is one of the leading causes of morbidity, mortality and hospitalization, worldwide. The immunomodulatory properties of clarithromycin reduce exacerbation, morbidity and mortality in patients with COPD. Clinical studies indicated that long term use of clarithromycin is efficacious in the treatment of COPD exacerbations with lower incidence of adverse effects. The present review suggests that clarithromycin can be used as a first line therapy in the management of mild or moderate COPD exacerbations.

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Disclosure

Dr. Agam Vora have declared and confirmed that there is no conflict of interest with respect to this authored publication.

References


Fig. 1: Levels of induced-sputum inflammatory markers in the clarithromycin and placebo groups before and after treatment. (AT = after treatment; BT = before treatment; IL-8 = interleukin-8; LTB4 = leukotriene B4; TNF-α = tumour necrosis factor-α. *p < 0.05 before versus after treatment)