

Clinical utility of Garenoxacin in Lower Respiratory Tract Infections: A Retrospective Analyzes: A Case-Cohort Study

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Abstract

Background: In the backdrop of community settings management of lower respiratory tract infections (LRTI) combined with significant comorbidities, exacerbated respiratory disease, recurrence and poor response to first-line antibiotics poses a therapeutic challenge. Antibiotic resistance of common LRTI pathogens including *Streptococcus pneumoniae* reported by Asia-pacific countries is among highest in the world. Newer fluoroquinolones with extended Gram-positive activity symbolize significant advance against penicillin-resistant *S. pneumoniae* (PRSP).

Aim: To assess clinical role of garenoxacin in LRTI.

Methods: Retrospective cohort analyzes of consecutive patients receiving garenoxacin for LRTI under community settings. Baseline demographics including symptoms, medical, and prior antibiotic usage history were noted. Clinical response was interpreted as success or failure specifying significant improvement or persistence of presenting symptoms, respectively. Adverse events requiring treatment withdrawal or alternative therapy were also noted.

Results: Garenoxacin was prescribed for Acute bronchitis (54%) acute exacerbation of chronic obstructive pulmonary disease (22%), Bronchiectasis (13%), and others as 1st line empiric therapy (59%), 2nd line therapy (11%) after failure of azithromycin for LRTI and as continuation therapy (30%) after i.v. antibiotics. Associated high-risk factors were present in 65% cases. Garenoxacin therapy was advised for 5-14 days in all cases established clinical success (100%) with no reported cases for serious adverse events. Assessed mean treatment duration for acute bronchitis/CAP and AECOPD were 7.9 and 7.1 days, respectively.

Conclusion: Management of AECOPD or LRTI in settings of significant comorbidities remains a therapeutic challenge. Garenoxacin a distinguished des-fluoroquinolone essays clinical advantage against PRSP and AECOPD/LRTI management, especially in the context of inadequate response to first-line therapy.

Key words: Exacerbation of chronic obstructive pulmonary disease, Fluoroquinolone, Lower respiratory tract infections, *Streptococcus pneumoniae*

INTRODUCTION

Lower respiratory tract infections (LRTI) are an extensive universal health problem. In terms of disease burden

LRTI amounts to 94,037,000 disability-adjusted life years (DALYs) lost globally according to the World Health Organization report and accounts for about 20% of total mortality due to infectious diseases in India.^{1,2}

LRTI is defined as an acute illness of ≤ 21 days presenting with a cough and one of the symptoms such as sputum production, dyspnea, wheeze, and chest pain/discomfort having no other explanation for symptoms. LRTI is broad term encompassing mainly acute bronchitis, CAP, acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and acute exacerbation of bronchiectasis.³

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Acute purulent bronchitis is characterized by infection of bronchial tree resulting into reversible bronchial inflammation, bronchial edema, and mucus formation.⁴ CAP is more severe infection than acute bronchitis having prolonged symptom course and higher risk for complications. Clinical diagnosis of CAP is made when symptoms of acute LRTI are present for <1 week; at least one systemic feature present like fever, chills, rigor; new focal sign on chest examination, and no other possible explanation for the symptoms.² COPD exacerbation and Bronchiectasis exacerbation compels adverse impact on systemic inflammation, lung functions, exercise performance, quality of life, associated comorbidities effecting higher morbidity and mortality rates; warrants management with antibiotic therapy along with other therapies. AECOPD is defined as the acute change in patient's baseline dyspnea, cough, or sputum beyond normal variability requiring a change in therapy according to the American Thoracic Society and European Respiratory Society (ERS). Bacterial infections are responsible for 70-75% cases. Bronchiectasis means permanent dilation of the bronchi and bronchioles due to the destruction of the muscles and elastic connective tissue triggered by an infection. Bronchiectasis exacerbations are defined as worsening of ≥ 4 symptoms such as sputum with the cough, dyspnea, fever, wheezing, physical resilience, fatigue, lung function, and radiological signs of infection.⁵⁻⁹

In community setup, common causative pathogens of LRTI includes Gram-positive, Gram-negative, and atypical. ERS, in collaboration with European Society for clinical microbiology and infectious diseases (ESCMID), recommends amoxicillin + clavulanate, fluoroquinolones and macrolides (in countries with low resistance) for the management of LRTI.³

Garenoxacin, a unique fluoroquinolone, lacks fluorine atom at C6 position which was thought to be essential, unlike traditional quinolones. Garenoxacin owing to unique substitutions at the 6th, 7th, and 8th position in quinolone ring essays lower MIC₉₀ and higher AUC/MIC₉₀ ratio governing higher potency, killing power, lower susceptibility to efflux, and resistance mechanisms against prevailing respiratory Gram-positive/negative and atypical pathogens including *Streptococcus pneumoniae* compared to other fluoroquinolones.^{10,11}

The current study was directed to evaluate the clinical performance of Garenoxacin for the management of LRTI.

METHODS

A case series cohort involving consecutive patients requiring fluoroquinolones or garenoxacin for LRTI

were analyzed, where cases were treated for LRTI at primary care center between July and September 2014. Database of all adult patients treated for LRTI at the respiratory clinic was inspected to identify cases. Diagnosis made by attending physician was noted. Furthermore, epidemiological data, demographic data, medical history, treatment history including prior use of antibiotics or fluoroquinolone, clinical response, and adverse event data were collated for analysis. Therapeutic response was adjudged as clinical success specifying complete resolution/significant improvement or failure specifying no significant improvement/persistence of symptoms with therapy. Serious adverse event (SAE) was defined as serious medical abnormality or hospitalization, disability, death, congenital anomaly. It was confirmed for any SAE to be reported to regional or central pharmacovigilance center.

Statistical Analyzes

Descriptive statistics was used to tabulate the data with percentage rate calculated for all categorical nominal and ordinal data variables.

RESULTS

During the rainy season month of July to September 2014, LRTI cases involving garenoxacin for management were distinguished and further analyzed.

Baseline Demographics

Analyzed 46 cases (Table 1) included male (71%), female (29%) with presenting complaints of fever (80%), cough (54%), dyspnea (44%), cough with expectoration (30%), chest pain (26%), swelling (26%), itching (9%), weakness (7%), rhinitis (2%), oral ulcer (2%), dysphagia (2%), anorexia (2%), and pulmonary edema (2%). In addition,

Table 1: Baseline demographic parameters of the study (n=46)

| | |
|---|---------------------------------|
| Average age | 48 years |
| Average weight | 49.4 kg |
| Study details | Number of patients n (%) |
| Gender | |
| Males | 32 (71) |
| Females | 13 (29) |
| Concomitant significant comorbidities | |
| Past history of tuberculosis | 14 (31) |
| Hypertension | 7 (15) |
| Type 2 diabetes | 6 (13) |
| Dyslipidemia | 3 (7) |
| Bronchial asthma | 3 (7) |
| Cardiovascular disease | 2 (4) |
| Hypothyroidism | 1 (2) |
| Concomitant risk factors | |
| Smoking | 8 (17) |
| Alcohol | 6 (13) |
| Hospitalization history in past 3 weeks | 4 (9) |

22% cases were sputum culture positive with *S. pneumoniae* being most commonly isolated bacteria. Concomitant significant comorbidities and risk factors present in 65% cases. Concurrent medications included mucolytic, inhaled bronchodilator, inhaled corticosteroid, oral hypoglycemic, anti-hypertensive, and hypolipidemic agents and others.

Clinical Results

Study cases (n=46) as diagnosed by physician incorporated as Acute bronchitis (54%), AECOPD (22%), Bronchiectasis (13%), pyopneumothorax (4%), Empyema (4%) and Pharyngitis/Tonsilitis (2%), highlighted in Figure 1. Garenoxacin was administered to these cases at a dose of 400 mg daily for 5-14 days. Complete resolution or significant improvement was noted for the majority of symptoms. Furthermore, laboratory data were available for 47% cases demonstrated notable improvement in total leukocyte and neutrophil count at day 5 of therapy compared to day 0. Clinical success was documented in 100% case with no reported case of therapy failure (Figure 2). All of the cases at day 5 of evaluation documents 96% clinical success signifying early clinical response with Garenoxacin therapy.

Garenoxacin was preferred as 1st line empiric therapy in 59% cases, 2nd line therapy after failure of Azithromycin for LRTI in 11% cases and as continuation therapy, i.e., switch over after piperacillin + tazobactam (17%), meropenem (7%), and other beta-lactam + beta-lactamase inhibitor combinations (6%) mainly for empyema, AECOPD and bronchiectasis in total 30% cases (Figure 3). Assessed mean duration of Garenoxacin therapy included 7.9 & 7.1 days for Acute bronchitis, AECOPD respectively as highlighted in Table2.

Safety Profile

None of the cases reported any adverse event or SAE requiring discontinuation of therapy or hospitalization.

DISCUSSION

Overwhelming morbidity and mortality of LRTI are representative of global health barrier posed by them. In community setup, common etiology of LRTI is Gram-positive/negative pathogen, especially *S. pneumoniae* most common pathogen succeeded by *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and atypical pathogens.³

In India, COPD a gradually progressive disease estimated to account for 22.2 million cases by 2016, disease burden rise of about 30% compared to 2006. In terms of Global burden, COPD will be the 7th leading cause of DALYs lost by 2030. COPD accounts for 56% of total health care costs

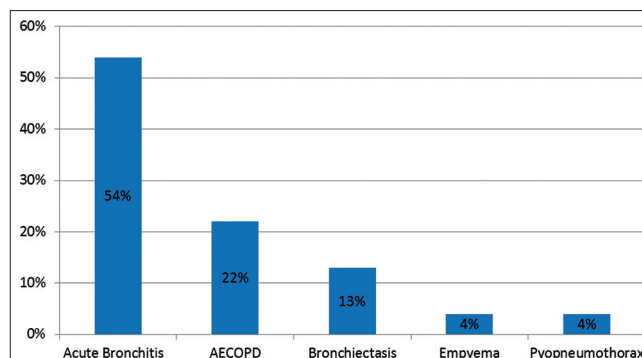


Figure 1 : Study cases (n=46) as diagnosed by physician

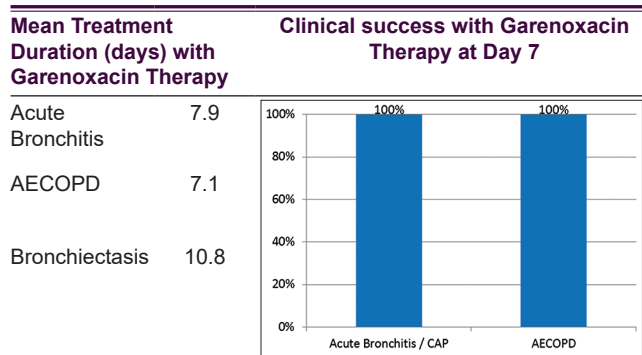


Figure 2: Clinical success with Garenoxacin therapy at day 7

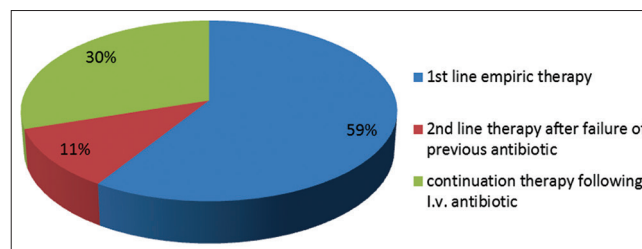


Figure 3 : Garenoxacin Therapy Preference

Table 2: Preferred treatment duration for Garenoxacin in patients with LRTI

| Days | Acute bronchitis (n=24) (%) | AECOPD (n=10) (%) |
|-------|-----------------------------|-------------------|
| ≤5 | 4 (17) | 1 (10) |
| 6-10 | 19 (79) | 9 (90) |
| 11-14 | 1 (4) | 0 (0) |

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease, CAP: Community-acquired pneumonia

due to respiratory diseases. In India, estimated economic burden of COPD is ≈35,331 crores which can be reduced to only 4,135 crores if we follow national and international treatment guidelines.^{12,13}

AECOPD is defined as the acute change in patient’s baseline dyspnea, cough, or sputum beyond normal day to day variations requiring a change in therapy. In India, estimated AECOPD burden is about 0.9 million

by 2016. Following hospitalization, AECOPD reports 5-year mortality rate of about 50%. AECOPD leads to an accelerated rate of lung function decline requiring several weeks to recover. RTIs are most common cause of AECOPD precipitation.^{12,13} In India, *Klebsiella pneumoniae*, *S. pneumoniae*, *S. aureus*, and *Pseudomonas aeruginosa* are common pathogen isolated from AECOPD patients.¹⁴⁻¹⁶ The treatment goal should be to minimize the impact of current episode and prevent future exacerbations. Global initiative for lung disease (GOLD) guidelines recommend pharmacotherapy with bronchodilators, corticosteroids, and antibiotics for AECOPD. Systemic antibiotics reduce recovery time, improves lung function (FEV₁) and arterial hypoxemia (PaO₂), reduce relapse rate, treatment failure, and length of hospital stay in AECOPD. A systemic review reports 77% reduction in short-term mortality, 53% reduction in treatment failure with antibiotics and supports antibiotics usage in moderate or severe AECOPD. GOLD guidelines recommend antibiotic usage in AECOPD patients with 3 cardinal symptoms such as increase in dyspnea, sputum volume, and sputum purulence for duration of 5-10 days.^{12,13}

A meta-analysis involving 19 randomized controlled trials (RCTs), and a therapeutic outcome probability model considers fluoroquinolone (moxifloxacin, levofloxacin) and amoxicillin + clavulanate equivalent with highest predicted efficacy for the management of AECOPD and acute exacerbation of chronic bronchitis (AECB).^{17,18} Compared to respiratory quinolones combination of amoxicillin + clavulanate requires longer therapy duration (i.e., 10 days compared to 5 days of quinolones) with higher reports of gastrointestinal intolerance especially at higher dosages.³

Amoxicillin + clavulanate is recommended as 1st line therapy by ERS and ESCMID guidelines for LRTI management.³ Clinical trial data are presented as the following format, reported efficacy parameter (sample size, efficacy evaluated at therapy day, the dosage of antibiotic). Randomized, double-blind, comparative controlled studies with amoxicillin + clavulanate for AECOPD/AECB management reports 88.8% success rate (728, day 7-14, 500/125 mg thrice daily, 7-14 days);¹⁹ 93.2% clinical success (600-500/125 mg thrice daily, 7 days); 87% clinical cure (287, day 10, 875 mg twice daily, 10 days);²⁰ 74.1% cure (310, day 9-11, 500/125 mg thrice daily, 8 days).²¹

Moxifloxacin, a 4th generation fluoroquinolone, according to a recent meta-analysis involving 11 RCTs is considered clinically equivalent and bacteriologically superior to comparator agents for AECOPD management.²² A analysis of 4 comparative studies for AECB/AECOPD reports 89% clinical response with Moxifloxacin.²³ In

randomized, double-blind, comparative controlled studies for AECOPD/AECB management moxifloxacin reports 89% clinical resolution (491, day 5, 400 mg once daily, 5-10 days);²⁴ 86.3% clinical cure rate at day 7 (345, day 10 ± 3, 400 mg once daily, 7 days);²⁵ and 83-87.6% clinical success (MOSAIC study) (730, day 7-10, 400 mg once daily, 5 days).²⁶ AVANTI a prospective, observational study involving 2536 AECB/AECOPD patients reported 93.2% improvement at 5 days.²⁷

Levofloxacin, a 3rd generation fluoroquinolone, in randomized, double-blind, comparative controlled studies for AECOPD/AECB management reports 82.8% clinical success rate (532, day 5, 500 mg once daily, 5 days);²⁸ 93% complicated/79.2% uncomplicated cases (763, day 3/5, 750 mg once daily, 3/5 days);²⁹ 82.8% clinical success (511, day 10, 500 mg once daily, 7 days);³⁰ and 96.5% cured (346, day 7, 500 mg once daily, 7 days).³¹

Though the novel respiratory fluoroquinolones offer substantial superior clinical benefit, their success has often been hampered by the presence of penicillin-resistant *S. pneumoniae* (PRSP) and quinolone-resistant *S. pneumoniae* (QRSP) strains in circulation. These strains are often resistant to multiple antibiotic classes.³ For AECOPD/AECB management, a randomized, double-blind (MAESTRAL) study involving 1372 patients reports failure rate of 22% with amoxicillin + clavulanate (875/125 mg twice daily, 7 days), 20.6% with moxifloxacin (400 mg once daily, 5 days) at 8 weeks and an observational study involving 260 patients reports 12.5% failure rate with both amoxicillin + clavulanate /moxifloxacin at 4 week.^{32,33}

A recent study reports worldwide 15-30% *S. pneumoniae* are multidrug-resistant, i.e., resistant to ≥3 antibiotic classes.³⁴ An Asian surveillance of CAP patients reports 52.6% *S. pneumoniae* non-susceptible to penicillin.³⁵ A surveillance from the United States reports rise of penicillin-resistant invasive *S. pneumoniae* serotype 19A from 6.7% in 1998 to 35% in 2005.³⁶ A PROTEKT surveillance study from the United states involving 39,495 isolates reports 21.2% isolates resistant to penicillin.³⁷ Global surveillance studies report 10-30% *S. pneumoniae* isolates harbors first step mutations conferring low-level fluoroquinolone resistance.³⁸ A multicenter study from Hong Kong reports 13.3% Levofloxacin and 8.9% moxifloxacin resistance with *S. pneumoniae*.³⁹

Garenoxacin a des-fluoroquinolone with novel structure essays lower MIC₉₀ and higher AUC/MIC₉₀ ratio amounting to higher potency, killing power and lower susceptibility to resistance mechanisms against extensive Gram-positive/negative and atypical pathogens including *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.^{10,11}

A prescription event monitoring study involving 11,698 patients comprised of 39% AECB patients reports 91.3% clinical success with Garenoxacin.⁴⁰ A review of RCTs by Takagi *et al.* reports 93% efficacy with Garenoxacin in AECB patients.¹⁰

According to various *in vitro* studies, Garenoxacin demonstrates lower MIC₉₀ against PRSP compared to moxifloxacin and levofloxacin. Garenoxacin demonstrates lower MIC₉₀, higher AUC/MIC₉₀ ratio, shorter time required to achieve 99.9% killing against *S. pneumoniae* mutants with single, double, or triple mutations in quinolone resistance determining region, i.e., QRSP and lower tendency to select resistant clones signifying better activity compared to moxifloxacin, levofloxacin against QRSP.⁴¹⁻⁴⁷ A review of RCTs by Takagi *et al.* reports 89% efficacy with Garenoxacin against PRSP.¹⁰

An *in-vitro* study involving 14,665 pneumococcal strains reports 8-32-fold greater activity with Garenoxacin compared to Levofloxacin, inhibition of >99.9% strains and >99.9% activity against *S. pneumoniae* strains resistant to 6 drug classes.⁴⁸ Another *in-vitro* study involving 18,887 *S. pneumoniae* isolates reports Garenoxacin potency of 16-32-fold superior than levofloxacin and 2-fold superior than Moxifloxacin.⁴⁹

Garenoxacin offers comprehensive efficacy of 91-96% against RTI with better safety profile established over ≈20,000 patient indexes. Garenoxacin shows efficacy of ≈94% against β-lactam or macrolide-resistant *S. pneumoniae* in clinical trials.^{10,50}

In the present study associated with comorbidities or risk factors were present in 65% cases which included mainly past history of Tuberculosis, Tye 2 DM, Hypertension, Smoking or Alcoholism. Past history of tuberculosis was present in AECOPD or Bronchiectasis cases mainly, and none of the patients were diagnosed to have active tuberculosis or were on concurrent anti-tuberculous therapy. Current retrospective analyzes report 100% clinical success with Garenoxacin for the LRTI management.

Current retrospective analyzes findings are exploratory and need to be further confirmed in multicenter, randomized, double-blind clinical trial for AECOPD.^{30,51}

CONCLUSION

AECOPD, a cause of significant health burden leads to very high mortality post hospitalization. RTIs are most common cause precipitation of exacerbation in COPD patients with *S. pneumoniae* as the most common responsible pathogen. Widespread use of beta-lactams governs rising prevalence

of PRSP. Fluoroquinolones remain preferred agents for the management of AECOPD, especially with associated significant comorbidities and risk factors. Garenoxacin des-fluoroquinolone with unique structure exhibits lower MIC₉₀ signifying better activity against common respiratory pathogens including PRSP, QRSP, and AECOPD or LRTI management compared to levofloxacin and moxifloxacin.

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