

A Case-Cohort Study on Clinical utility of Garenoxacin mesylate in Respiratory Tract Infections: A Retrospective Analyses

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Abstract

Background: Clinical management of respiratory tract infections (RTI) in community settings remains a therapeutic challenge with the overbearing threat of antimicrobial resistance looming large, especially amongst Gram-positive organisms including *Streptococcus pneumoniae*. The new generation fluoroquinolones reflect a significant advance with clinical utility often delineated for patients with recurrent infections or with comorbid risk factors.

Aim: To assess the clinical role of fluoroquinolones or garenoxacin for RTI in community settings.

Methods: This retrospective case series study conducted during monsoon period comprised of patients receiving fluoroquinolones including garenoxacin for RTI. Patients were assessed subjectively for control of baseline symptoms. Therapeutic response was judged as a clinical success or failure signifying significant improvement or no significant improvement/persistence of symptoms respectively. Observed notable or serious adverse events (SAE) were collected for analyses.

Results: Retrospective analyses revealed 22 patients receiving garenoxacin as first-line empiric therapy amongst fluoroquinolone prescriptions for RTI. Significant comorbidities were associated in 64% cases. Garenoxacin therapy advised for 5 days in all cases established clinical success (100%) and failure (0%) with no reported cases of any SAE.

Conclusion: For management of RTI especially in settings of associated significant comorbidities fluoroquinolones remains empiric choice. Garenoxacin a novel des-fluoroquinolone presents clinical utility in RTI while offering high safety profile.

Key words: Fluoroquinolones, Garenoxacin, Levofloxacin, Moxifloxacin, Respiratory tract infection

INTRODUCTION

Respiratory tract infections (RTI) are major global health problem in adult males and females. According to World Health Organization (WHO) report disease burden of RTI is estimated at 94,037,000 disabilities adjusted life years (DALYs) and 3.9 million deaths. While disease burden of lower RTI (LRTI) and upper RTI (URTI) is estimated at 90,748,000 DALYs and 1,815,000 DALYs, respectively.¹

In India, according to WHO data LRTI accounted for 35.1/100,000 population deaths in 2008 and accounted for 20% of total mortality due to infectious diseases.²

Sinusitis is an important cause of URTI. Infectious Disease Society of America (IDSA) 2012 clinical practice guidelines for acute bacterial rhinosinusitis, recommends fluoroquinolones (levofloxacin, moxifloxacin) as an alternative for initial empirical antimicrobial therapy, while macrolides, 2nd and 3rd generation cephalosporin are no longer recommended.³ European respiratory society and European society for clinical microbiology and infectious diseases recommends fluoroquinolones (levofloxacin, moxifloxacin) as alternate empirical therapy for community-acquired LRTI especially in setting of relevant bacterial resistance.⁴ IDSA/American thoracic society consensus guidelines on management of

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www.ijss-sn.com

Month of Submission : 08-2015
Month of Peer Review : 09-2015
Month of Acceptance : 10-2015
Month of Publishing : 10-2015

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community-acquired pneumonia in adults recommends fluoroquinolones as empirical treatment for outpatient treatment in presence of significant comorbidities, use of antimicrobials in previous 3 months or high-level macrolide resistance.⁵

Most common adverse effects associated with fluoroquinolones use are gastrointestinal (nausea, vomiting, diarrhea), central nervous system (CNS) (headache, dizziness), allergic (rash, pruritus). Less common but important adverse effects of fluoroquinolones include QTc prolongation, blood glucose alterations, hepatotoxicity, phototoxicity, peripheral neuropathy, and seizures.⁶

Garenoxacin a novel des-fluoroquinolone with modified structure activity relationship provides broad spectrum coverage against common respiratory Gram-positive, Gram-negative and atypical pathogens including *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis*. While offering lower minimum inhibitory concentration (MIC₉₀) values, and higher area under the curve (AUC)/MIC₉₀ ratio against the majority of pathogens.^{7,8} Efficacy and safety of garenoxacin has been well-documented in ≈20,000 patient database. Overall garenoxacin shows efficacy of 91-96% in RTI with highly established safety profile.^{7,9,10}

The present study was conducted to evaluate retrospectively the clinical role of fluoroquinolones or garenoxacin in the management of RTIs while being prescribed as an empirical therapy in RTI.

METHODS

A retrospective case series cohort was analyzed to evaluate the role of fluoroquinolones including garenoxacin as an empirical therapy for adults with RTI. Cases were identified from database of all adult patients who were treated for RTI between August and October 2014, where the provisional diagnosis was made by attending physician. Case of URTI and LRTI were identified as diagnosed by physician. Epidemiological, demographic, medical history, prior history of antibiotic or fluoroquinolone use, treatment, clinical outcome and adverse event data was gathered for analyses. Therapeutic response was judged as clinical success or failure signifying significant improvement or no significant improvement/persistence of symptoms respectively at the end of therapy. Serious adverse event (SAE) defined as hospitalization or prolonged hospitalization, disability, death, congenital anomaly, or medical abnormality of significance was confirmed to be reported to central or regional pharmacovigilance center by the doctor.

Statistical Analyses

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

RESULTS

During the monsoon season of August to October 2014, 48 cases of RTI treated with various fluoroquinolones involving Garenoxacin were identified. Amongst these 48 cases, all of the RTI cases treated with Garenoxacin mesylate ($n = 22$) were further analyzed.

Baseline Demographics

Out of 22 cases analyzed 82% were male and 18% were female (Table 1). Associated significant comorbidities were noted in 41% cases which included dyslipidemia, diabetes, and hypertension. Two cases had past history of treatment for tuberculosis. Associated concomitant risk factors were noted in 27% cases which included history of smoking and alcohol consumption. Concomitant medications included oral hypoglycemic, antihypertensive and hypolipidemic agents. None of the cases were prescribed antibiotics or fluoroquinolones other than garenoxacin. None of the cases had history of hospitalization or fluoroquinolone use in recent past.

Clinical Results

The cases included in the study presented with the complaints of fever (100%), cough (95%), expectoration (41%), breathlessness (23%), and dysphagia (5%). Garenoxacin was administered to these cases at a dose of 400 mg daily for 5-7 days. Complete resolution was noted in fever (91%), cough (100%), expectoration (100%), breathlessness (100%), and dysphagia (100%).

Therapy with garenoxacin was advised for 5 days in all cases. Clinical success was noted in all cases at the end of 5 days therapy. No case of therapy failure was reported (Figure 1). Detailed analyses of baseline symptomatology and clinical response after 5 days therapy in URTI and LRTI cases are detailed in Figures 2 and 3.

Table 1: Baseline demographic parameters of the study

Total number of patients - 22	
Average age - 51.1 years	Average weight - 67.6 kg
Study details	Number of patients n (%)
Gender	
Males	18 (82)
Females	4 (18)
Medical history	
Dyslipidemia	2 (9)
Diabetes	3 (14)
Hypertension	4 (18)

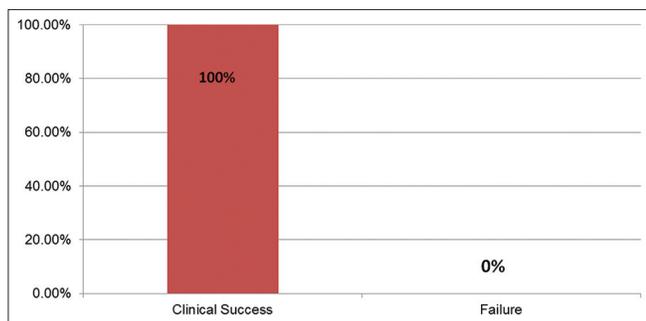


Figure 1: Clinical response for URTI at end of 5 days of therapy

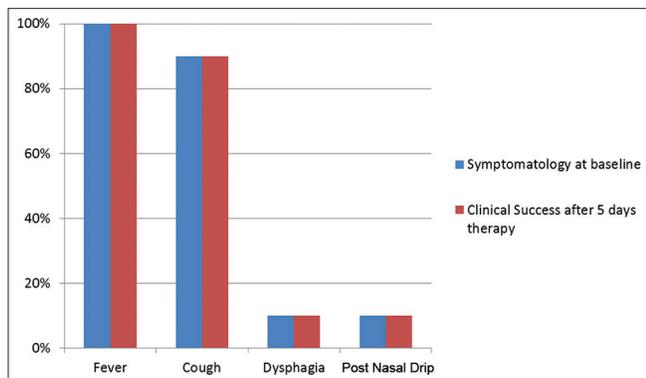


Figure 2: Clinical response for URTI (n=10) symptoms with therapy

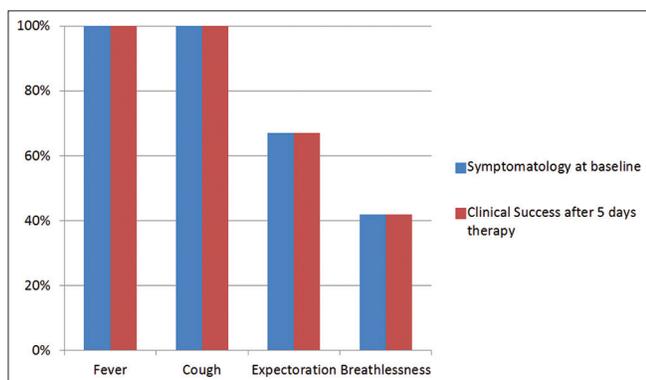


Figure 3: Clinical response for LRTI symptoms with therapy

Safety Profile

None of the cases reported any adverse event or SAE, which required discontinuation of therapy or hospitalization.

DISCUSSION

RTIs are global health problem leading to significant morbidity and mortality. RTIs accounts for 6.4% of total global disease burden in terms of DALYs.¹ Fluoroquinolones (levofloxacin, moxifloxacin) use amongst frontline agents for empirical therapy of URTI and LRTI in community settings is well documented in literature and also advised by leading respiratory disease

treatment international guidelines. Empirical therapy of RTI in community settings with fluoroquinolones is especially advised in settings of associated significant comorbidities, high-level relevant bacterial resistance and use of antimicrobials in previous 3 months.³⁻⁵

Garenoxacin a novel des-fluoroquinolone lacks fluorine atom at C6 position unlike other fluoroquinolones with additional methyl isoindolyl and difluoromethoxy substitutions at C7 and C8 position respectively. Garenoxacin offers wide spectrum coverage against Gram-positive, Gram-negative and atypical pathogens including common respiratory pathogens like *S. pneumoniae*, Hemophilus influenza and Moraxella catarrhalis; while offering lower MIC₉₀ values, and higher AUC/MIC₉₀ ratio against majority of pathogens, that has important bearing for clinical efficacy while preventing resistance amongst Gram-positive pathogens including *S. pneumoniae*.^{7,8} Garenoxacin shows efficacy of 91-96% in RTI over ≈20,000 patients database. Garenoxacin shows clinical efficacy of ≈94% in β-lactam resistant and macrolide resistant *S. pneumoniae*, most common pathogen responsible for RTI.^{7,9,10}

In the presents study, associated significant comorbidities were present in 64% cases which included diabetes (14%), hypertension (18%), dyslipidemia (9%), smoking (23%), and alcohol (5%). In the present retrospective analyses garenoxacin demonstrates clinical success of 100% while being prescribed as empirical therapy for RTI in community settings.

Most common adverse effects associated with fluoroquinolones use are gastrointestinal, CNS, allergic while less common but important includes QTc prolongation, blood glucose alterations, hepatotoxicity, phototoxicity, peripheral neuropathy, seizures.⁶ Recent years various fluoroquinolones were withdrawn from the U.S. market because of serious adverse drug effects includes gatifloxacin (dysglycemia), sparfloxacin (QTc prolongation, phototoxicity).¹¹

Clinical safety of levofloxacin has been well established over large data from various clinical trials and postmarketing surveillance studies. Amongst these 7,537 phase 3 clinical trials patients database reported adverse reactions with levofloxacin includes gastrointestinal disorders nausea (7%), diarrhea (5%), vomiting (2%), constipation (3%), abdominal pain (2%), dyspepsia (2%); Nervous system disorders headache (6%), dizziness (3%), insomnia (4%); and others (>0.1 to <1) includes cardiac disorders (palpitation, ventricular tachycardia, ventricular arrhythmia); metabolism disorders (hyperglycemia, hypoglycemia).¹² QTc prolongation may result potentially life-threatening ventricular arrhythmia like torsade de pointes.¹¹ There is a

recent report of QTc prolongation with 16.7% incidence in patients on levofloxacin involving 2,176 patients.¹³ Similarly, there are reports of significant dysglycemia with levofloxacin.^{14,15} A retrospective cohort study reported levofloxacin ($n = 457,994$), crude incidence rates for severe hyperglycemia 0.18 per 1000 cases, while amongst diabetic patients odds ratio hyperglycemia with levofloxacin compared to azithromycin was 1.8.¹³ Furthermore, there are sporadic reports of serious CNS effects with levofloxacin like 2 case reports of seizures and 1 case report of catatonia.¹¹

Clinical safety of moxifloxacin is also well established based in large clinical trials and postmarketing surveillance data. Amongst these 14,981 phase 2-4 clinical trials patients evaluated for moxifloxacin gastrointestinal disorders nausea (7%), diarrhea (6%), vomiting (2%), constipation (2%), abdominal pain (2%), dyspepsia (1%); nervous system disorders headache (4%), dizziness (3%), and insomnia (2%) have been reported.¹⁶ Simultaneously, there have been several nested case-control studies have suggested cardiac adverse events including arrhythmia with moxifloxacin or metabolic dysfunction involving hyperglycemia/dysglycemia.¹⁷⁻²⁰ A nested case-control analyses from cohort of 605,127 patients identified risk of serious arrhythmia with moxifloxacin (RR = 3.30).¹⁹ Amongst the new 3rd and 4th generation fluoroquinolones moxifloxacin carries greater risk of QT prolongation.¹¹ A population-based cohort study involving diabetic patients published reported moxifloxacin ($n = 4,221$) absolute risk of hyperglycemia was 6.9 per 1000 persons respectively. Adjusted odds ratio for moxifloxacin compared with macrolides for hyperglycemia was 2.48.²⁰

Clinical safety of garenoxacin is well established over $\approx 20,000$ patients involving various clinical trials and postmarketing surveillance data. A postmarketing surveillance conducted in Japan involving 6,412 patients reported total adverse reactions (3.45%) with garenoxacin includes gastrointestinal disorders (0.87%) nausea (0.06%), diarrhea (0.48%), vomiting (0.05%), nervous system disorders (0.20%), cardiac disorders (0.20%), and Metabolism disorders (0.20%).⁹ A prescription event monitoring study involving 12,498 patients from 400 centers reported total adverse events (1.27%) includes diarrhea (0.13%), CNS side effects (0.06%), nausea and/or vomiting (0.5%), rash (0.02%), abnormal liver function test (0.02%) and dysgeusia (0.01%).¹⁰ With no reports of torsade de pointes over database.^{9,10}

CONCLUSION

Fluoroquinolones are suitable agents for empiric therapy of RTI in community settings. Garenoxacin, a structurally

modified des-fluoroquinolone offers higher potency against common respiratory Gram-positive, Gram-negative and atypical pathogens while offering lowest MIC₉₀ against most of pathogens and high AUC/MIC₉₀ ratio, an indicator of fluoroquinolone potency. High safety profile of garenoxacin is well-documented over database of $\approx 20,000$ patients, offers differentiated safety profile amongst fourth generation fluoroquinolones for broader clinical use in real world settings.

ACKNOWLEDGMENT

The authors would like to thank Ms. Gauri Sondkar, Ms. Nilofer Allarakha and Mr. Akshay Mahapatra for their assistance required in the conduct of the study.

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How to cite this article: Padmanaban A, Krishnaprasad K, Lathi S, Bhargava A. A Case Cohort Study on Clinical utility of Garenoxacin mesylate in Respiratory Tract Infections: A Retrospective Analyses. *Int J Sci Stud* 2015;3(7):136-140.

Source of Support: Nil, **Conflict of Interest:** None declared.