

# A Case Cohort Study on Clinical Utility of Garenoxacin Mesylate in Recurrent Uncomplicated Urinary Tract Infections: A Retrospective Analyses

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## Abstract

**Background:** Recurrent urinary tract infections (UTIs) are important health issue in both females and males with greater implication on patients quality of life. *Escherichia coli* is most common causative agent of UTIs. Fluoroquinolones are often looked upon as empiric therapy for recurrent UTIs.

**Aim:** Retrospective analyses to assess the clinical utility of fluoroquinolones in recurrent UTIs.

**Methods:** This retrospective case series cohort study comprised of patients suffering from recurrent UTIs who received fluoroquinolones including garenoxacin. Clinical response or success was judged by subjective assessment for control of presenting symptoms while assessing change in laboratory parameters. Failure was defined as persistence of symptoms or no significant improvement. Any notable side effects or serious adverse events (SAE) observed were also collected for analyses.

**Results:** Retrospective analyses amongst fluoroquinolone cases revealed 41 patients receiving garenoxacin as first line therapy after being diagnosed with recurrent UTIs. Therapy with garenoxacin was advised for 5 or 7 days in 49% and 49% cases respectively. Clinical success was established in all patients in both the treatment groups. No case of therapy failure was reported. None of the cases reported any SAE.

**Conclusion:** Fluoroquinolones remains empiric therapy for recurrent UTIs in setting of resistance to other antibiotics. Garenoxacin is a structurally modified new generation quinolone offering clinical utility in recurrent UTIs with better safety profile.

**Key words:** Fluoroquinolones, Garenoxacin, Urinary tract infection

## INTRODUCTION

Recurrent urinary tract infections (UTIs) are significant health issue in both females and males<sup>1</sup> with the diagnosis and management of recurrent UTIs in clinical settings also remaining a therapeutic challenge. Epidemiological surveillance studies estimates prevalence of recurrent UTI 20.9% over 6 months and 44% over 1-year period in women.<sup>2</sup> Recurrent UTI is defined as 2 episodes of UTI in last 6 months or  $\geq 3$  episodes of UTI in last 12 months in females and more than one episode of UTI in males

after the treatment and complete resolution of the previous symptomatic infection.<sup>3-5</sup> Frequency of sexual intercourse is most important risk factor for recurrent UTI in young female and others include age at first UTI  $\geq 15$  years, maternal history of UTIs, new sexual partner in the past year and spermicide use in past year.<sup>6</sup> Uncomplicated UTIs are less frequent in males because of factors like longer urethra, larger distance between anus and urethral meatus, antibacterial properties of prostatic secretions. Thus, UTIs in adult male are believed to indicate underlying pathology.<sup>5</sup>

Clinical features of uncomplicated UTIs includes burning micturition with dysuria, frequency of urination, urgency and pain.<sup>7</sup> Worldwide, most common causative agents of uncomplicated UTI includes *Escherichia coli* (75%), *Klebsiella pneumoniae* (6%), *Staphylococcus saprophyticus* (6%) and others (13%).<sup>8</sup> Various Indian studies also identifies *E. coli* as the most common causative agents of UTI.<sup>9-11</sup> Appropriate

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use of trimethoprim/sulfamethoxazole, nitrofurantoin, fluoroquinolones and  $\beta$ -lactam antibiotics is recommended for treatment of recurrent UTIs.<sup>6</sup> According to a large scale *in vitro* surveillance data resistance rates of *E. coli* isolates from female outpatients were trimethoprim/sulfamethoxazole (17.5%), ampicillin (38%) and that of fluoroquinolones (<4%).<sup>12</sup> Fluoroquinolones are therefore often looked upon as an empiric choice of drugs especially in recurrent UTIs for both male and female in settings of high resistance to other antibiotics. Recurrent cystitis suggested treatment includes 7 days therapy with fluoroquinolones.<sup>6,13</sup>

Garenoxacin a novel desfluoroquinolone with modified structure activity relationship offers dual inhibition against bacterial DNA gyrase and topoisomerase IV, thus requiring mutations in both the enzymes for resistance to occur and also offers broad spectrum coverage against Gram-positive, Gram-negative or Enterobacteriaceae while offering lower minimum inhibitory concentration 90% (MIC<sub>90</sub>) values compared to other fluoroquinolones.<sup>14,15</sup>

The present study was conducted to evaluate retrospectively the clinical utility of fluoroquinolones in management of UTIs while being prescribed as an empirical antibiotic therapy in UTIs.

## METHODS

A retrospective case series cohort was analysed to evaluate role of fluoroquinolones including garenoxacin as an empirical therapy for adults with UTIs. Cases were identified from database of all adult patients who were treated for UTIs between August and December 2014, where the provisional diagnosis was made by attending physician. Case of UTI was defined as patient with  $\geq 1$  symptoms of dysuria, increased frequency of micturition, urgency, hesitancy, lower back pain, lower abdominal pain.<sup>16</sup> Dysuria was defined as pain, burning or discomfort on urination.<sup>17</sup> Amongst these cases recurrent UTI was defined as patient with  $\geq 2$  episodes in last 6 months for both males and females. Epidemiological, demographic, medical history, prior history of antibiotic or fluoroquinolone use, treatment, clinical outcome and adverse event data was gathered for analyses. Additionally cases with intact laboratory data in terms of urine microscopy and urine culture were further analysed. Therapeutic response was assessed as clinical success or complete resolution signifying significant improvement or complete resolution of symptoms at the end of therapy. Failure was defined as persistence of symptoms or no significant improvement. 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 Analysis

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

## RESULTS

Between August and December 2014, 90 cases of uncomplicated UTIs were identified. Amongst these 90 cases,  $\beta$ -lactam or fluoroquinolones were advised in 30 and 60 cases of uncomplicated UTI. All of the recurrent UTI cases ( $n = 41$ ) treated with garenoxacin mesylate were further analysed (Figure 1).

## Baseline Demographics

Out of 41 cases analyzed 49% were male and 51% were female (Table 1). Associated significant comorbidities were noted in 41% cases which included diabetes and hypertension. There was no history of functional urinary tract abnormalities and tuberculosis. Associated concomitant risk factors were noted in 66% cases which included history of smoking and alcohol consumption. Concomitant medications included oral hypoglycemic agents and anti-hypertensives, none of the cases were prescribed antibiotics or fluoroquinolones other than garenoxacin. None of the cases had history of hospitalization or were prescribed fluoroquinolones for treatment of previous episodes of UTI.

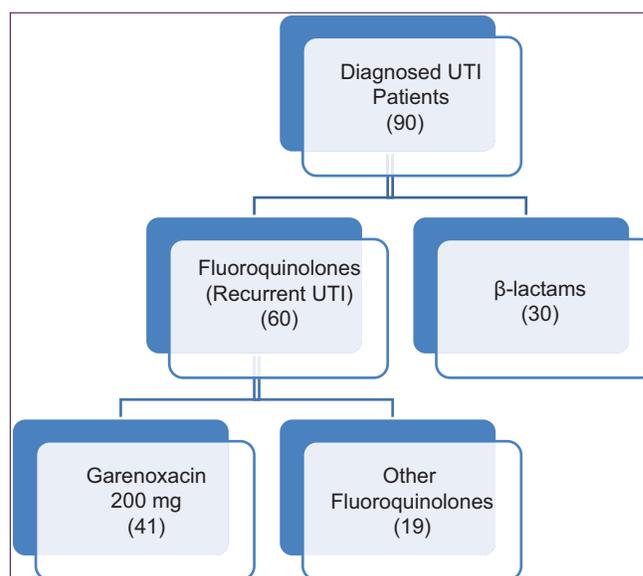


Figure 1: Therapy of choice for uncomplicated urinary tract infections

**Table 1: Baseline demographics and clinical data for the study population receiving garenoxacin**

Total number of cases	41
Mean age	39.2 years
Mean weight	65.8 kg
Gender (%)	
Males	20 (49)
Females	21 (51)
Medical history (%)	
Diabetes	7 (17)
Hypertension	10 (24)
Clinical features (%)	
Dysuria	41 (100)
Increased frequency of urination	21 (51)
Lower abdominal pain	13 (32)
Laboratory parameters (%)	
Pyuria (>10 WBCs/hpf)	41 (100)
Hematuria (>3 RBCs/hpf)	8 (19.5)
Urine culture	8 (19.5) ( <i>E. coli</i> )

*E. coli*: *Escherichia coli*, WBCs: White blood cells, hpf: High power field, RBC: Red blood cells

### Clinical Results

The cases included in the study presented with the complaints of dysuria (100%), increased frequency of urination (51%), hesitancy (29%), itching (34%), fever (100%), chills (41%), lower back pain (36.5%), lower abdominal pain (32%), foul smell (2.5%). Pyuria defined as >10 white blood cells/high power field (WBCs/hpf) was noted in all cases (100%) at baseline.<sup>18</sup> Microscopic hematuria defined as >3 red blood cells (RBCs)/hpf was noted in 19.5% cases at baseline.<sup>19</sup> Baseline urine culture revealed *E. coli* isolates in 19.5% cases (Table 1). Garenoxacin was administered to these cases at a dose of 200 mg for 5-7 days. Complete resolution of pyuria (all cases <5 WBCs/hpf) and microscopic hematuria (all cases nil RBCs/hpf) was documented in all cases at end of suggested duration of therapy.

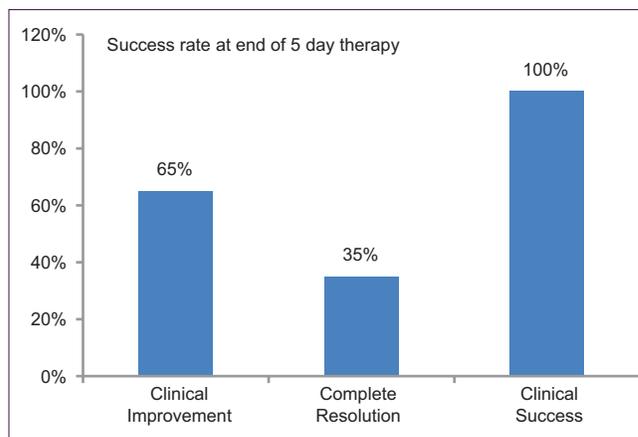
Therapy with garenoxacin was advised for 5 or 7 days in 49% and 49% cases respectively. Clinical success was noted in all cases at the end of both 5 and 7 days therapy. Also, 1 case required 14 days therapy to establish complete resolution. No case of therapy failure was reported (Figures 2 and 3).

### Safety Profile

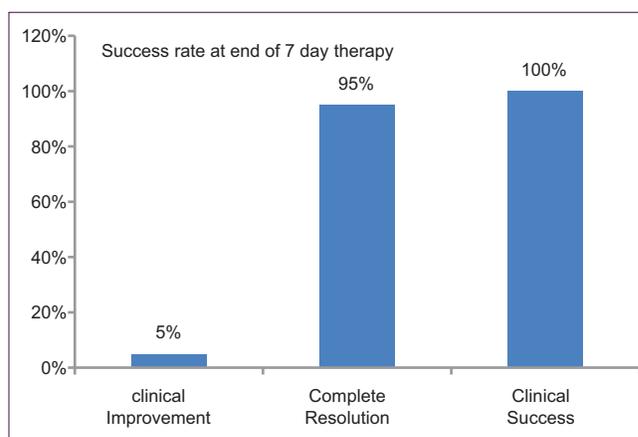
None of the cases reported any adverse event or SAE, which required discontinuation of therapy or hospitalization.

## DISCUSSION

Recurrent UTIs are important health issue in both females and males.<sup>1</sup> Majority cases of recurrent UTIs are due to reinfection (>80%) and also includes relapse cases. Reinfection is recurrent UTI with previously isolated



**Figure 2: Clinical response with 5 day therapy for garenoxacin**



**Figure 3: Clinical response with 7 days therapy for garenoxacin**

bacteria or other bacteria after treatment with negative urine culture. Reinfections are believed to occur from extraurinary sites like vagina and rectum. Relapse is recurrent UTI with the same organism within 2 weeks after adequate therapy.<sup>6</sup> Further, uropathogenic *E. coli* invades urothelial cells and forms quiescent intracellular bacterial reservoirs or intracellular bacterial community which can explain reinfection with genetically identical bacterial strain, bacterial persistence and recurrence of UTIs.<sup>24</sup> A systemic review for the diagnostic accuracy of uncomplicated UTI signs and symptoms estimates sensitivity with dysuria (80%), increased frequency (88%), urgency (67%), lower abdominal pain (50%) and specificity with fever (92%), hematuria (85%), flank pain (69%) and lower abdominal pain (50%).<sup>7</sup>

Management guidelines of recurrent UTIs includes a course with trimethoprim/sulfamethoxazole or fluoroquinolones (ofloxacin, ciprofloxacin, norfloxacin).<sup>6</sup> Treatment guidelines suggest recurrent cystitis should be managed with pretreatment urine culture and 7 days fluoroquinolone therapy.<sup>13</sup> The study findings are consistent with respect to management of recurrent UTIs as suggested in the guidelines.

Garenoxacin a novel fluoroquinolone offers unique structure activity relationship at position 8 in the form of difluoromethyl ether linkage offering high potency against Gram-negative pathogens including Enterobacteriaceae causing UTI.<sup>20</sup> Garenoxacin offers lowest MIC<sub>90</sub> values amongst fluoroquinolones against most of these common uropathogens. Garenoxacin demonstrates urinary excretion of 41.8% and believed to exhibit bactericidal action against uropathogens, while demonstrating lower MIC<sub>90</sub> values including *E. coli* (0.06 mcg/ml), *K. pneumoniae* (0.5 mcg/ml), *S. saprophyticus* (0.06 mcg/ml), *Proteus mirabilis* (1 mcg/ml) compared to other fluoroquinolones.<sup>14,15</sup>

Garenoxacin was also found to be superior in terms of safety profile. A post-marketing surveillance study done at Japan by Hori and Maki in 6412 patients confirmed the superior tolerability profile of garenoxacin with minimal or negligible incidence of gastrointestinal, cardiovascular or central side effects.<sup>21</sup>

The findings of this retrospective analysis are exploratory and need to be further confirmed in larger multicenter, randomized, double blind clinical trial settings especially for recurrent uncomplicated UTI or pyelonephritis cases.

## CONCLUSION

Fluoroquinolones are suitable alternative for uncomplicated or recurrent UTIs. Garenoxacin, a structurally modified fluoroquinolone offers higher potency against Gram-negative or Enterobacteriaceae uropathogens. Clinical success reported in present study with garenoxacin in recurrent UTIs is well backed by optimal pharmacokinetic and pharmacodynamic parameters demonstrated with garenoxacin including high urinary excretion rate and lower MIC<sub>90</sub> values against the uropathogens.

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