Efficacy and safety of oral gemifloxacin for the empirical treatment of pneumonia

Vindu Amitabh, Anish Singhal, Sudhir Kumar, Narmada Patel, Yasir S. Rizvi, Pankaj Mishra
Departments of Medicine and Nephrology, Safdarjung Hospital, New Delhi, India

ABSTRACT

Context: Respiratory tract infections (RTI) are common causes of morbidity and mortality worldwide. Initial antibiotic therapy in upper and lower respiratory tract infections is usually empirical. The increasing evidence of antibacterial resistance in the pathogens commonly associated with pneumonia has raised concerns about the efficacy of currently available therapies and poses a challenge to clinicians. Gemifloxacin is a synthetic fluoroquinolone antimicrobial agent exhibiting potent activity against most Gram negative and Gram positive organisms. Hence, this study was planned to evaluate the efficacy of gemifloxacin as an empirical therapy in pneumonia. Materials and Methods: This was an open labelled, single-arm study. Patients with clinical features of community acquired pneumonia (CAP) who fulfilled the inclusion criteria received treatment with oral gemifloxacin 320 mg once daily for 5-7 days. Once enrolled in the study, patients were treated as outpatient or as inpatient depending on clinical need. The primary efficacy was to evaluate the clinical response at the end of therapy, i.e., day 9-11 for CAP. Secondary efficacy parameters included radiological and bacteriological response at the end of therapy. Patients were evaluated three times during the entire course of treatment (Visit 1, Day 0; Visit 2, Day 2-4; Visit 3, Day 9-11) for their clinical, radiological and/or bacteriological response, as well as for safety assessment. Results: A total of 105 patients received the study medication (gemifloxacin 320 mg orally). Two patients were “lost to follow-up” and one patient had to discontinue medication due to insufficient therapeutic effects. Clinical response at the end of therapy was successful in 99 (96.1%) while clinical failure was reported in 4 (3.9%) patient. As per the radiological response, 77.1% of the total cases showed improvement, 8.6% had no change, and 2.9% cases had deterioration in radiological findings. Gemifloxacin is an effective drug in the management of CAP. Conclusions: Gemifloxacin with coverage against both Gram positive and Gram negative organisms as well as atypical pathogens, with once daily oral dosing and minimum side effect is a very effective and economical choice for treating CAP empirically.

Key words: Community acquired pneumonia, gemifloxacin, outcomes

INTRODUCTION

Community acquired pneumonia (CAP) is a common cause of morbidity and mortality worldwide. In India, approximately 9.5% of the total population suffers from respiratory tract infections. Initial antibiotic therapy in upper and lower respiratory tract infections in usually empirical, focused towards the most common etiologic agents, which include Streptococcus pneumoniae, Klebsiella pneumonia, Hemophilus influenza, and Moraxella catarrhalis. The decreasing susceptibility pattern of these pathogens, particularly S. pneumoniae, to antibacterials has raised concerns about the decreasing efficacy of currently available therapies. In the US, almost 100% of clinical M. catarrhalis isolates produce beta-lactamase and up to 50% of H. influenza isolates produce beta-lactamase. Penicillin resistant strains have been identified worldwide and resistance to other antibacterials such as cephalosporins and macrolides is increasing among isolates of S. Pneumoniae. Thus, the efficacy of therapy with antibacterials such as the penicillins, cephalosporins, and macrolides may be compromised.

The increasing evidence of antibacterial resistance in the pathogens commonly associated with Respiratory
tract infections (RTI) has therefore raised concerns about the efficacy of currently available therapies in CAP. New agents with broad spectrum of activity against the range of organisms implicated in CAP are therefore needed.

Gemifloxacin is a novel synthetic broad-spectrum fluoroquinolone that exhibits bactericidal activity primarily by inhibiting bacterial DNA gyrase. Topoisomerases IV of the bacteria is another target of the drug. Gemifloxacin has excellent activity against both gram-negative and gram-positive organisms including potent antibacterial activity against Streptococcus species and Staphylococcal species. Hence, this study was planned to evaluate the efficacy of gemifloxacin as empirical therapy in pneumonia.

**MATERIALS AND METHODS**

This was an open labelled, single-arm study. Patients with clinical features of CAP who fulfilled the inclusion criteria received treatment with oral gemifloxacin 320 mg once daily for 7-10 days. Once enrolled in the study, patients were treated as outpatients or as inpatients depending on clinical need.

**Inclusion criteria**

1. Male or female patients aged 18-70 years having given their informed consent.
2. Clinically and radiological confirmed cases of community acquired pneumonia (CAP).
3. Patients who had at least one respiratory sign or symptoms like cough, throat irritation, purulent sputum production, dyspnoea.
4. Female patients of child bearing potential having a negative urine pregnancy test prior to enrolment (including those who were practicing birth control, those with tube ligation and those less than 1 year post menopausal).
5. Patients having given written consent to participate in the study.

**Exclusion criteria**

1. Females who were pregnant, lactating, planning a pregnancy or of childbearing potential and not using an accepted method of contraception.
2. Hypersensitivity to quinolone or any member of quinolone class of antibacterials.
3. Patients with other chronic pulmonary disease like cystic fibrosis, active tuberculosis, bronchiectasis, or active pulmonary malignancies.
4. Patient with a life threatening or serious underlying disease, which is unstable, e.g. Myocardial infarction
5. Patients with known or suspected renal impairment and/or known creatinine clearance < 40 ml/min.
6. Patients with ALT, AST, or alkaline phosphatase levels greater than 3 times the upper limit of normal.
7. Patients who were immunocompromised including HIV positive patients.
8. Patients with history of epilepsy, myasthenia gravis, drug addiction.
9. Patients with a clinical history or evidence of hemolytic crisis, G6PD deficiency, tendonitis, prolongation of QTc interval.
10. Patients receiving Class IA or Class III anti-arrhythmic agents or steroids.
11. Patient requiring parenteral antibacterial therapy for any other condition other than CAP.

**Duration of therapy**

**CAP: Seven to ten days treatment**

Patients were evaluated three times during the entire course of treatment (Visit 1, Day 0; Visit 2, Day 2-4; Visit 3, Day 7-9 and Visit 4, Day 9-11) for their clinical, radiological and/or bacteriological response, as well as for safety assessment.

**RESULTS**

**Efficacy and safety parameter**

The primary efficacy was to evaluate the clinical response at the end of therapy, i.e., day 9-11 for community acquired pneumonia (CAP). Secondary efficacy parameters included 1) radiological response at the end of therapy 2) bacteriological response at the end of therapy.

The safety end point was to evaluate the incidence of adverse effects and laboratory parameters.

Data on a continuous scale was expressed as a mean along with standard deviation. Categorical data was expressed as percentage. Comparative statistical analysis was carried out using ANOVA in respect of data measured on a continuous scale and using non parametric ANOVA in respect of data measured on ranking scale. All differences with P value below 0.05 were labelled as statistically significant.

**Key demographic data**

A total of 105 patients received the study medication (gemifloxacin 320 mg orally). All the subjects received at least one dose and were therefore included for safety analysis. Two patients were lost to follow-up and one patient had to discontinue medication due to insufficient therapeutic effects. The age of patients ranged from 18-70 years with an average of 48.21 years. Mean weight and height of subjects were within normal limits. Of the total subjects treated 58% were male and remaining 42% were female subjects [Table 1].

**Data analysis and efficacy results**

Clinical response among 103 patients at the end of therapy was successful in 99 (96.1%), while clinical failure was reported in 4 (3.9%) patient. A detailed account of primary efficacy parameters used to analyze the overall clinical outcome is shown in Table 2.

Results reveal that mean respiratory rate was 23.31 at baseline level, which after treatment at 2-4 days had
significantly fallen by 12.1% and at end of treatment by 25.8% from baseline level. Mean temperature was 100.08°F at baseline level which after treatment at 2-4 days was 98.55°F, which was a significant reduction and at end of treatment average temperature was 98.27°F. There was no significant change in mean diastolic blood pressure. Analysis shows that 82.8% of the total cases had fever and 48.6% had chills at baseline level. After the treatment at the end of 2-4 days only 8.6% of the cases had fever and 11.4% had chills, which was significant reduction from baseline level.

Of the total, 74.0% and 92.0% had rales and cough, respectively, at baseline level. After the treatment at the end of 2-4 days, only 2.8% of cases had cough and 20.0% had rales, which was significant reduction from base line level. Of the total, 60.0% and 63.0% had dyspnoea and tachypnoea at baseline level. After the treatment at the end of 2-4 days, tachypnoea had a significant fall, i.e., 51.4% and dyspnoea showed a significant fall, i.e., 42.8% from baseline level. In the study group, 21.2% cases had hypoxemia and 48.6% had chest pain at baseline level. After the treatment at the end of 2-4 days, significant fall was observed in chest pain and significant reduction in hypoxemia at the end of 9-11 days. In the study group, 80.0% and 86.0% had pulmonary consolidation and sputum respectively at baseline level. After the treatment at the end of 2-4 days, both signs had significant fall from baseline level.

Secondary efficacy parameters
According to the bacteriological outcome in Table 3, 84.5% cases were clinically cured and hence could not expectorate sputum, required for bacteriological analysis at the end of therapy. They were classified under ‘unable to determine’. About 13.5% of the patients had eradication and in 2% there was a bacteriological persistence.

As per the radiological finding in Table 4, 77.1% of the total cases showed improvement, 8.6% had no change; 2.9% cases had deterioration in radiological findings. In 11.4% outcome was “unable to determine”.

SAFETY RESULTS

Laboratory investigations
None of the patients experienced vital signs of potential clinical concern or reported any adverse events during the course of study. Only one patient had increase in the value of alkaline phosphatase, which was considered unrelated to study medication. The drug was found to be safe and well tolerated in all treated patients [Table 5].

DISCUSSION

Community-acquired pneumonia (GAP) is the cause of substantial morbidity, mortality, and resource utilization worldwide. Despite substantial progress in therapeutic options, CAP remains a significant cause of morbidity and death, and there continues to be a major controversy concerning the antimicrobial management of this infection.[9] The mixed etiology and the changing susceptibility of pathogens causing CAP, in particular that of Streptococcus pneumoniae, has created a challenge, in some circumstances, to clinicians as to which therapeutic approaches may be the most appropriate in terms of optimal patient outcome.[10] Initial antimicrobial therapy is normally given empirically, before the bacterial cause of the infection can be determined in the laboratory, and in many cases treatment is empirical throughout due to the lack of reliable microbiological data. An understanding of the possible pathogens and resistance patterns is helpful in guiding antibiotic choice, and a detailed knowledge of the local susceptibility of the potential pathogens would ensure
Table 5: Laboratory investigations

| Parameters (Units) | Baseline level | End of Rx |
|--------------------|----------------|-----------|
| Hemoglobin (g/dl)  | 12.84 ± 2.07   | 67.13 ± 13.20 | 0.74 ± 0.69 |
| Haematocrit (%)    | 33.45 ± 14.64  | 35.27 ± 13.16 | 22.48 ± 10.14 |
| Platelet Count (+10^11/mm^3) | 237.10 ± 95.76 | 247.84 ± 77.03 |
| Neutrophils (%)    | 67.13 ± 13.20  | 64.13 ± 11.56 | 0.45 ± 0.70 |
| Lymphocytes (%)    | 22.48 ± 10.14  | 25.11 ± 7.55 | 7.29 ± 9.24 |
| Monocytes (%)      | 7.39 ± 9.24    | 7.21 ± 10.11 | 12.84 ± 2.07 |
| Eosinophils (%)    | 3.96 ± 6.96    | 4.91 ± 9.21  | 35.27 ± 13.16 |
| Basophils (%)      | 0.38 ± 0.84    | 0.45 ± 0.70  | 111.09 ± 48.6 |

Clinical Chemistry

| Alkaline Phosphatase (U/L) | 212.74 ± 121.55 | 203.80 ± 126.4 |
| AST (U/L)                  | 28.96 ± 11.09   | 27.95 ± 14.88 |
| ALT (U/L)                  | 29.11 ± 9.27    | 28.07 ± 10.40 |
| BUN (mg/dl)                | 30.51 ± 15.45   | 28.33 ± 10.46 |
| Albumin (g/dl)             | 4.33 ± 0.72     | 4.32 ± 0.56  |
| Serum Bilirubin (mg/dl)    | 0.81 ± 0.71     | 0.74 ± 0.69  |
| Serum Protein (g/dl)       | 7.34 ± 0.80     | 7.28 ± 0.65  |
| Creatinine (mg/dl)         | 0.96 ± 0.27     | 0.93 ± 0.23  |
| Glucose (mg/dl)            | 111.09 ± 48.6   | 108.8 ± 52.3 |

Penicillin-resistant S. pneumoniae (PRSP) has become a great problem. PRSP is a widespread problem, with rates of resistance ranging from 5% to 80% in various parts of the world. Risk factors for infection with PRSP strains include young age, day-care center attendance, prior administration of antimicrobial agents, and severe underlying diseases. It is likely that, in cases in which isolates have intermediate or low-level resistance to penicillin, the drug concentrations achieved in serum and in the lungs are adequate to eradicate these strains. However, strains for which the minimum inhibitory concentrations (MICs) of penicillin are higher (≥ 4 mg/L) may affect outcomes, and therapeutic failures are more likely to be seen as more strains with high-level penicillin resistance emerge.

As the use of non-penicillin antimicrobials has increased, so has the development of resistance to these agents among S. pneumoniae. Worldwide rate of macrolide resistance has risen dramatically in recent years. The prevalence of resistance is highly variable between countries, ranging from < 3% to > 70%.

The new fluoroquinolones (Amitabh et al., 2011) display excellent bioavailability and have longer serum half-lives than ciprofloxacin allowing for once daily dose administration. Clinical trials comparing the new fluoroquinolones to each other or to standard
therapy have demonstrated good efficacy in a variety of community-acquired respiratory infections. Gemifloxacin is an antimicrobial agent that is used for treatment of community-acquired pneumonia and acute exacerbation of chronic bronchitis.\textsuperscript{[15–17]} Gemifloxacin, in contrast to other quinolones, demonstrated improved activity against Streptococcus pneumoniae and similar activity against gram-negative respiratory pathogens (\textit{Hemophilus influenzae}, \textit{Moraxella catarrhalis}) and atypical pathogens such as \textit{Chlamydia pneumoniae}, \textit{Legionella pneumophila}, and \textit{Mycoplasma pneumoniae}. It has insufficient activity against methicillin-resistant \textit{S. aureus} and cannot be used for such infections. It can be used as a once-daily dose drug as a result of its long half life.

Our study has shown excellent result in CAP patients treated with gemifloxacin (320 mg). Clinical response among 103 patients at the end of therapy was successful in 99 (96.1%) while failure was reported in 4 (3.9%). Analysis of secondary efficacy parameter reveals 84.5% were clinically cured and hence could not expectorate sputum required for bacteriological analysis at the end of therapy. These were classified as “unable to determine”. Another 13.5% of the patients had eradication and in 2% there was bacteriological persistence. As per radiological outcome 77.1% of the total cases showed improvement, 8.6% had no change and 2.9% had deterioration in radiological findings.

Several fluoroquinolones have either been withdrawn from the market or had their use severely restricted because of adverse effects [Table 6].

The remaining fluoroquinolones such as gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin have adverse effect profiles similar to ciprofloxacin Gemifloxacin is well tolerated; the frequency of adverse events with this agent is low. In this study none of the patients experienced any significant adverse drug reaction. Blood biochemical parameters were largely unaffected except statistically insignificant rise in the value of alkaline phosphatase. In other studies also most adverse events are mild-to-moderate in severity, with diarrhea, nausea and rash (< 3%), and headache (< 2%) most commonly reported. Drug interactions with gemifloxacin are not common, although absorption is greatly reduced when given with divalent and trivalent cation-containing compounds, such as antacids.

### CONCLUSIONS

Gemifloxacin is effective in patient showing resistance to macrolides, B-lactam, 3\textsuperscript{rd} generation cephalosporins and quinolones like Levofloxacin, Ciprofloxacin, and Ofloxacin. Amongst quinolones also it scored over equipotent trovafloxacivies due to no hepatotoxicity like the latter. Rightly it has been termed as respiratory fluoroquinolone and it is considered the only agent effective against multidrug resistant \textit{S. pneumonia} (DRSP, i.e., resistant to two or more of the following antibiotics – penicillin, 2\textsuperscript{nd} generation cephalosporin, macrolides, tetracycline, and co-trimoxazole). Besides, gemifloxacin is effective against atypical pathogens like \textit{M. pneumoniae}, \textit{E. pneumonia} and \textit{L. pneumophila}. Gemifloxin is therefore the true broad spectrum agent most suited for empiric therapy of CAP. It has no major side effects and drug-drug interaction with commonly co-prescribed drugs like Digoxin, theophylline antacids, etc are negligible. Clinical response among 103 patients at the end of therapy was successful in 99 (96.1%) while failure was reported in 4 (3.9%). It was not associated with any drop out of patient due to adverse effect. Gemifloxacin is a good efficacious, well tolerated economical drug for empirical treatment of CAP.

### REFERENCES

1. S Broor, MK Lalitha, R Chaudhry, RS Maitreyi, N Nisar, A Pandey, et al. Acute lower respiratory tract infections in India. Indian J Med Microbiol 1999;17:4-9.
2. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:527-72.
3. Tielejeh IM, Tielejeh HM, Heijal R, Mentoni VM, Baddour LM. The impact of penicillin resistance on short-term mortality in hospitalized adults with pneumococcal pneumonia: A systematic review and meta-analysis. Clin Infect Dis 2006;42:788-97.
4. Allen KD. Penicillin-resistant pneumococci. J Hosp Infect 1991;17:3-13.
5. Falco C, Almirante B, Jordano Q, Calonge L, del Valle O, Pigrau C, et al. Influence of penicillin resistance on outcome in adult patients with invasive pneumococcal pneumonia: Is penicillin useful against intermediate resistance strains? J Antimicrob Chemother 2004;54:481-8.
6. Appelbaum PC. World-wide development of antibiotic resistance in pneumococci. Eur J Clin Microbiol 1987;6:367-77.
7. Wierzbowski AK, Nichol K, Laing N, Hinsagata T, Nikulin A, Carlowsky JA, et al. Macrolide resistance mechanisms among Streptococcus pneumoniae isolated over 6 years of Canadian Respiratory Organism Susceptibility Study (CROSS) (1998 - 2004). J Antimicrob Chemother 2007;60:733-40.
8. Yoo BK, Triller DM, Yong CS, Lodise TP. Gemifloxacin: A new fluoroquinolone approved for treatment of respiratory infections. Ann Pharmacother 2004;38:1226-35.
9. Pagain F, Liienthal F, Bourdin A, Lugagne N, Tixier F, Génin R, et al. Severe community-acquired pneumonia: Assessment of microbial aetiology as mortality factor. Eur Respir J 2004;24:779-85.
10. Oncu S, Erdem H, Palsha A. Therapeutic options for pneumococcal pneumonia in Turkey. Clin Ther 2005;27:674-83.
11. Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: Implications for management guidelines. Thorax 2001;56:296-301.
12. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med
Amitabh, et al.: Oral gemifloxacin for treatment of pneumonia

13. Jokinen C, Heiskanen I, Juvonen H, Kallinen S, Kleemola M, Koskela M, et al. Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland. Clin Infect Dis 2001;32:1141-54.

14. Ball P. Quinolone generations: Natural history or natural selection? J Antimicrob Chemother 2000;46:17-24.

15. Bhavnani SM, Andes DR. Gemifloxacin for the treatment of respiratory tract infections: In vitro susceptibility, pharmacokinetics and pharmacodynamics, clinical efficacy, and safety. Pharmacotherapy 2005; 25:717-40.

16. Ball P, File TM, Twynholm M, Henkel T. Efficacy and safety of gemifloxacin 320 mg once-daily for 7 days in the treatment of adult lower respiratory tract infections. Int J Antimicrob Agents 2001; 18:19-27.

17. File TM Jr, Mandell LA, Tillotson G, Kostov K, Georgiev O. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: A randomized, multicentre, double-blind study. J Antimicrob Chemother 2007; 60:112-20.

How to cite this article: Amitabh V, Singhal A, Kumar S, Patel N, Rizvi YS, Mishra P. Efficacy and safety of oral gemifloxacin for the empirical treatment of pneumonia. Lung India 2012;29:248-53.

Source of Support: Nil, Conflict of Interest: (If present, give more details): None declared.