Prulifloxacin: a brief review of its potential in the treatment of acute exacerbation of chronic bronchitis

Francesco Blasi
Stefano Aliberti
Paolo Tarsia
PierAchille Santus
Stefano Centanni
Luigi Allegra

Institute of Respiratory Diseases, University of Milan, Fondazione IRCCS Policlinico-Mangiagalli-Regina Elena Milano, Italy; Institute of Lung Disease, Respiratory Unit, San Paolo Hospital, Milan Italy

Abstract: Exacerbations of chronic bronchitis (AECB) are a major cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD), and their impact on public health is increasing. The new fluoroquinolones have an excellent spectrum providing cover for the most important respiratory pathogens, including atypical and “typical” pathogens. Not surprisingly, different guidelines have inserted these agents among the drugs of choice in the empirical therapy of AECB. The pharmacokinetic and dynamic properties of the new fluoroquinolones have a significant impact on their clinical and bacteriological efficacy. They cause a concentration-dependent killing with a sustained post-antibiotic effect. This review discusses the most recent data on the new fluoroquinolone prulifloxacin and critically analyses its activity and safety in the management of AECB.

Keywords: prulifloxacin, exacerbations, chronic bronchitis

Introduction

Chronic bronchitis is estimated to affect between 3.7% and 6.8% of the population in Europe (Ball and Make 1998), and prevalence increases with age (McGuire et al 2001). Patients with chronic bronchitis are predisposed to recurrent attacks of bronchial inflammation—termed acute exacerbations of chronic bronchitis (AECB)—characterized by increased cough, worsening dyspnea, and changes in sputum purulence and volume (Anthonisen et al 1987). Infectious agents are estimated to account for around 80% of these episodes, with the remaining 20% attributed to noninfectious causes such as inadequate medical treatment, congestive heart failure, pulmonary embolism, etc (Sethi 2000). Patients with recurrent exacerbations are exposed to frequent courses of antimicrobials with a possible selection of antimicrobial resistance among common bacterial pathogens. Antibacterial therapy for AECB is aimed at relieving symptoms, preventing loss of pulmonary function that may lead to hospitalization, speeding recovery, and prolonging the time to the next exacerbation.

Fluoroquinolones are widely used antibiotics for the treatment of AECB due to their excellent pharmacokinetic/dynamic properties, high antimicrobial activity, and low incidence of side-effects (Blasi et al 2003).

We will review the available data on prulifloxacin efficacy and tolerability in the treatment of AECB. The review is based on a PUBMED literature search, using as keyword “prulifloxacin”, for original articles and reviews published in English from January 1990 to April 2006. Thirty-five articles were retrieved, 15 articles on urinary tract infections or strictly preclinical studies were discarded, and 20 papers were analysed.

Pharmacokinetic and pharmacodynamic features

Prulifloxacin (6-fluoro-1-methyl-7-[4-[(5-methyl-2-oxo-1, 3-dioxol-4-yl)methyl]-1-piperazinyl]-4-oxo-1H, 4H-[1, 3]thiazeto[3, 2-a]quinoline-3-carboxylic acid), the prodrug
of ulifloxacin, is a broad-spectrum oral fluoroquinolone antibacterial agent. After absorption, prulifloxacin is metabolized by esterases to ulifloxacin. Prulifloxacin is absorbed mainly from the upper small intestine and then metabolized to ulifloxacin in the liver by an α-esterase (paraoxonase) (first pass or presystemic metabolism) (Tougou et al 1998).

Table 1 shows pharmacokinetic characteristics of prulifloxacin (Picollo et al 2003; Matera 2006). Ulifloxacin concentrations in serum and lung have been recently evaluated (Concia et al 2005). In this open label study 27 patients with lung carcinoma requiring surgical intervention were recruited. A single dose of prulifloxacin 600 mg was administered and concentrations evaluated at 2, 4, 6, 12, or 24 hours preoperatively. Ulifloxacin concentrations in plasma and lung tissue were determined by reversed-phase high-performance liquid chromatography. The results reported show lung tissue levels higher than plasma levels, however values appear to be widely dispersed. At time 2, 4, 6, 12, and 24-hour the values ranges (lung tissue after correction for blood contamination) were 1.02–5.98, 1.39–4.59, 0.33–5.27, 0.46–3.63, and 0.28–3.0, respectively. The mean lung/plasma concentration ratio was 6.9 ± 0.6 (standard error) reflecting the wide dispersion of concentration values.

Good intracellular penetration in macrophages and human polymorphonuclear cells has been reported (Ozaki et al 1996). Ulifloxacin strengthens the phagocytic and microbicidal activities of the peritoneal macrophages against Klebsiella pneumoniae (Tullio et al 2000). When intracellularly concentrated, ulifloxacin can kill the bacteria directly or make them more susceptible to the phagocyte bactericidal effect (Tullio et al 1999). Moreover, ulifloxacin seems to modulate human polymorphonuclear (PMN)’s in vitro synthesis of proinflammatory cytokines such as interleukin (IL)-8, IL 1β, and tumor necrosis factor-α (TNFα) (Reato et al 2004).

### Drug interactions

In healthy volunteers co-administration of theophylline and prulifloxacin induces an increase of 15% theophylline area under the curve (AUC) and a 15% reduction of clearance (Fattore et al 1998). Likewise the other fluoroquinolones, cation-containing antacid, and iron preparations reduce absorption of prulifloxacin, these drugs should be administered 3 hours before or 2 hours after prulifloxacin (Keam et al 2004; Prats et al 2006).

### Microbiology

Ulifloxacin, the active metabolite of prulifloxacin, shows a wide spectrum of activity against Gram-positive and Gram-negative bacteria. In this review we will address the activity against the main respiratory pathogen involved in exacerbations of chronic bronchitis. As stated in a recent paper by Roveta and colleagues (2005), due to the absence of a defined breakpoint for prulifloxacin/ulifloxacin all the data are referred to ciprofloxacin breakpoint. This clearly hampers the clinical interpretation of the susceptibility data.

The activity against Streptococcus pneumoniae seems to vary considerably between studies. In three of these studies the ulifloxacin activity against S. pneumoniae resulted in fairly low minimum inhibitory concentration (MIC) values ranging from 0.12 to >4 µg/ml, with a MIC required to inhibit the growth of 90% of organisms (MIC90) value of >4 µg/ml (Ozaki et al 1991; Yoshida and Mitsuhashi 1993; Prats et al 2002).

In their study, Prats and colleagues showed a MIC50 of ulifloxacin of 1 µg/ml against the penicillin-susceptible strains and 2 µg/ml for those presenting moderate and high resistance; the MIC90 was 4 µg/ml for the penicillin-sensitive and intermediate strains and 2 µg/ml for the highly resistant strains (Prats et al 2002).

Another study, performed on 36 Italian strains, showed a better activity with MIC values ranging from 0.015 to 2 µg/ml and a MIC90 value of 1 µg/ml (Montanari et al 2001).

Ulifloxacin in vitro activity against strains of methicillin-susceptible Staphylococcus aureus is fairly good with a reported MIC90 value of <0.5 µg/ml (Montanari et al 2001; Prats et al 2002). No activity was demonstrated against methicillin-resistant strains.

The spectrum of activity mainly addresses Gram negative bacteria, including Pseudomonas aeruginosa.

Roveta and colleagues (2005) performed a susceptibility study on 300 clinical isolates. Using ciprofloxacin breakpoint, 72% of the strains were susceptible and prulifloxacin resulted in the most powerful available antipseudomonal fluoroquinolone with MIC values ranging from 0.015 to 128 µg/ml and a MIC90 of 16 µg/ml.

### Table 1 Pharmacokinetic characteristics of prulifloxacin (active metabolite ulifloxacin)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>T max (h)</th>
<th>C max (µg/ml)</th>
<th>Protein binding (%)</th>
<th>T½ (h)</th>
<th>AUC∞ (µg h/ml)</th>
<th>Clearance (ml/min·kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>600</td>
<td>1</td>
<td>2</td>
<td>41–59</td>
<td>10</td>
<td>8</td>
<td>170</td>
</tr>
</tbody>
</table>

**Abbreviations:** AUC∞, area under the plasma concentration time curve from time 0 to infinity; C max, maximal concentration; T max, time to reach maximal concentration; T½, half-life.
In this study time–kill tests at 4× MIC confirmed the pronounced bactericidal potency of the drug against *P. aeruginosa*. Amongst the members of the fluoroquinolone class assessed, prulifloxacin produced the lowest mutant prevention concentration (MPC) values (≤4 µg/ml).

Ulifloxacin activity against *Enterobacteriaceae* is one of the best among fluoroquinolones, with MIC₉₀ values ranging from 0.015 to 0.25 µg/ml.

*Haemophilus influenzae* and *Moraxella catarrhalis* are both highly susceptible to ulifloxacin with a MIC₉₀ always lower than 0.12 µg/ml.

No data are reported in the literature on the activity against *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, though Keam and Perry (2004) report unpublished data on a limited activity of ulifloxacin against *C. pneumoniae*.

**Clinical study**

One study has been published on the activity of prulifloxacin in AECB indication (Grassi et al. 2002). This double-blind, double-dummy, randomized study compared prulifloxacin 600 mg once daily with ciprofloxacin 500 mg twice daily for 10 days. The study was performed in 18 French and 7 Italian centers. A total of 235 patients (117 prulifloxacin and 118 ciprofloxacin) with Anthonisen I and II exacerbations of chronic bronchitis were enrolled (Anthonisen et al. 1987). The clinical response at the end of treatment was assessed as: (i) cure (resolution of all baseline symptoms), (ii) improvement (decrease in intensity of all symptoms), and (iii) failure (no decrease in the intensity of at least one symptom detected at baseline). The primary parameter for the evaluation of efficacy was the clinical outcome. Clinical cure or improvement were considered as therapeutic success.

Ninety-four patients (50 in prulifloxacin and 44 in ciprofloxacin group) had a microbiological evaluation on sputum culture. The bacteriologic response was based on the result of the sputum culture at the end of treatment as compared with baseline and was assessed as follows: (i) eradication (the pathogen observed at baseline was not found at endpoint); (ii) presumed eradication (absence of sputum sample because the patient was clinically improved); (iii) persistence (presence of causative organism at the end of therapy); (iv) superinfection (a new organism at the end of therapy, regardless of whether the original pathogen was present). Eradication and presumed eradication were considered a microbiological success.

Two hundred and twenty-one patients (94%) completed the study. Table 2 shows clinical and microbiological results. One or more drug-related adverse events were reported by 15.4% (18/117) and 12.7% (15/118) patients in prulifloxacin and ciprofloxacin group, respectively. The most common treatment-related adverse event in both treatment groups was gastric pain, reported by 10/117 (8.5%) and 8/118 (6.8%) patients in prulifloxacin and ciprofloxacin group, respectively.

One unpublished study comparing prulifloxacin with amoxicillin–clavulanate is reported in three reviews (Keam and Perry 2004; Cazzola et al. 2006; Prats et al. 2006), and another unpublished dose-finding study by Cazzola and colleagues (Cazzola et al. 2006).

These two studies will not be described in the present review as they are not published.

**Safety and tolerability**

Limited data are reported in the literature on tolerability of prulifloxacin in the treatment of respiratory infections. In the Grassi and colleagues (2002) study the pattern and incidence (around 10%–15%) of adverse reaction were similar in prulifloxacin and ciprofloxacin treated patients, and mainly related to gastrointestinal disturbances. In their review, Prats and colleagues (2006) report on some data on file concerning phototoxicity. They describe a cross-over study on healthy volunteers that showed comparable effects with that of ciprofloxacin. Two studies address the potential cardiotoxicity of prulifloxacin (Lacroix et al. 2003; Akita et al. 2004). Both

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical and microbiological results in patients with exacerbations of chronic bronchitis treated with prulifloxacin 600 mg once daily or ciprofloxacin 500 mg twice daily for 10 days (modified from Grassi et al. 2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Prulifloxacin (110 patients)</strong></td>
</tr>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>(MITT population)</td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>15.3%</td>
</tr>
<tr>
<td>Improvement</td>
<td>69.4%</td>
</tr>
<tr>
<td>Failure</td>
<td>15.3%</td>
</tr>
<tr>
<td><strong>Microbiological outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>(94 patients, 50 prulifloxacin and 44 ciprofloxacin)</td>
<td></td>
</tr>
<tr>
<td>Eradication/Presumed eradication (overall)</td>
<td>88.7%</td>
</tr>
<tr>
<td><strong>Main pathogens:</strong></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>17/19</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>8/9</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>5/5</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>4/5</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>5/5</td>
</tr>
</tbody>
</table>

International Journal of COPD 2007:2(1)
these studies show negligible effects on cardiac depolarization/repolarization cycle in vitro and in vivo indicating a very low probability of Qc interval prolongation.

**Positioning of prulifloxacin in the treatment of AECB**

Isolation of bacteria from sputum samples and the distal airways using a protected specimen brush (Fagon et al 1990; Soler et al 1998) has identified *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* as the predominant respiratory pathogens in patients with AECB, with *H. influenzae* being identified most frequently (in 30%–70% of all episodes). Other bacteria identified in bronchial samples include the atypical pathogens *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*, which have been implicated either as the sole causative agent or as co-pathogens in approximately 5%–15% of acute exacerbations (Blasi et al 1993; Mogulkoc et al 1999). The nature of the causative pathogen tends to vary according to the severity of the underlying chronic bronchitis and the degree of lung function impairment.

Official or unofficial guidelines for the classification and antibacterial treatment of AECB and/or exacerbations of COPD are available in a number of countries.

The treatment choice usually depends on a number of factors, including suspected or confirmed aetiology, clinical features and history, and local patterns of antibacterial resistance. Other relevant factors include the tolerability, convenience, and cost of treatment. Two additional criteria for antibacterial selection should be taken into account, the ability of the antibacterial to penetrate bronchial tissue and mucus, and low ecological risk (ie, a low propensity to induce resistance). Across the guidelines, patients with chronic bronchitis or COPD presenting with symptoms of an acute exacerbation are usually stratified into three groups. The first group of patients presents with ≥2 Anthonisen criteria, but generally have only mild to moderate impairment of lung function (forced expiratory volume in one second \(\text{FEV}_1\) >50% of the predicted value), no comorbidities and <3 exacerbations/year. A second group of patients is characterized by the presence of additional risk factors for treatment failure, which include moderate to severe lung function impairment (\(\text{FEV}_1\) >35%–<50% of the predicted value) and/or significant comorbidity (eg, cardiac disease, diabetes, hepatic/renal insufficiency) and/or frequent exacerbations (≥4/year). Patients considered at the highest risk for treatment failure are included in the third group and often demonstrate very severe impairment of lung function (\(\text{FEV}_1\) <35% of the predicted value) and/or multiple risk factors (including significant comorbidity, chronic corticosteroid therapy) and frequent exacerbations (≥4/year).

This kind of patient stratification is also related to the bacterial flora associated with the exacerbations.

Thus, in patients with mild to moderate chronic bronchitis, *H. influenzae* and *S. pneumoniae* are the most commonly isolated bacteria during AECB, while *Staphylococcus aureus* and Gram-negative bacteria, including *Pseudomonas aeruginosa* and *Enterobacteriaceae* species, are predominantly isolated from patients with a severe degree of airflow obstruction (\(\text{FEV}_1\) <35% of the predicted value) (Eller et al 1998; Miravitlles et al 1999).

Notwithstanding the paucity of published clinical data, the antimicrobial spectrum and the results of Grassi and colleagues (2002) study seem to indicate the possible role of prulifloxacin in the treatment of exacerbations of outpatients with moderate to severe COPD, which are generally caused by Gram-negative bacteria (mainly *Haemophilus influenzae*, *Enterobacteriaceae*, and *Pseudomonas* spp.

**Conclusions**

Prulifloxacin is a new fluoroquinolone with indications in the treatment of urinary tract infection and acute exacerbations of chronic bronchitis. The antibacterial spectrum is similar to that of ciprofloxacin with clear advantages in terms of antipseudomonal in vitro activity. Only few data on pharmacokinetic and pharmacodynamic characteristics, including bronchial and lung tissues, have been published. The available data indicate a fairly good penetration into the lung tissue with high intracellular concentrations in phagocytes and PMNs, with an interesting “immunomodulatory” activity. The only published AECB treatment study shows a clinical and microbiological activity comparable with ciprofloxacin.

More data are clearly required to better evaluate the role of this new fluoroquinolone in the panorama of antibiotics.

**References**


