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Review

Prulifloxacin: A new fluoroquinolone for the treatment of acute exacerbation of chronic bronchitis

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Abstract

Empiric therapy with oral antibiotics is normal practice in the treatment of acute exacerbations of chronic bronchitis (AECB), but there is growing concern regarding efficacy of the currently available antimicrobials. Prulifloxacin, the lipophilic prodrug of ulifloxacin, is an oral fluoroquinolone antibacterial agent with a broad-spectrum in vitro activity against Gram-negative and -positive bacteria, and a long elimination half-life, which allows the once-daily administration. In addition, it penetrates extensively into lung tissues. Statistical analyses indicated a significant linear trend between the prulifloxacin 300, 450, and 600 mg doses, which would point to an interesting relationship between dose employed and response obtained. The 600 mg once-daily dose showed the best risk/benefit ratio, and was selected for use in the pivotal clinical trials. In well-designed clinical trials, prulifloxacin 600 mg administered once daily for 10 days in patients with AECB showed good clinical and bacteriological efficacy (similar to that of ciprofloxacin or co-amoxiclav). In particular, the clinical response rates were favourable in all clinical trials, with eradication rates in patients with pneumococcal infections at least as high as the comparators. It can be concluded that prulifloxacin 600 mg once daily is a new therapeutic prospect in the antimicrobial therapy of AECB. In particular, since good patient compliance is a key factor in the successful treatment of any infection, the once daily treatment with prulifloxacin may have some compliance advantages compared to the twice-daily treatment with agents such as ciprofloxacin or co-amoxiclav.

Keywords: Acute exacerbation of chronic bronchitis; Co-amoxiclav; Ciprofloxacin; Prulifloxacin

Contents

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1. Introduction

The ideal antibiotic for treatment of acute exacerbations of chronic bronchitis (AECB) should be clinically and microbiologically effective, capable of inducing a long remission period, improving patients' well-being and satisfaction, decreasing the need for visits, hospitalizations, additional drugs, and causing a lower incidence of resistant bacteria [1]. Fluoroquinolones have been broadly accepted for the treatment of AECB because of their specific pharmacokinetic properties, high antimicrobial activity, and low incidence of side-effects [2].

2. Characteristics of prulifloxacin that make it useful for the treatment of AECB

Prulifloxacin, the lipophilic prodrug of ulifloxacin [3], is an oral fluoroquinolone antibacterial agent with a broad-spectrum in vitro activity against various Gram-negative and -positive bacteria commonly associated with lower respiratory tract infections [4].

After oral administration, prulifloxacin is rapidly and extensively metabolized to ulifloxacin, the active moiety. Ulifloxacin has an extended elimination half-life, ranging from 10.6 to 12.1 h after single-dose prulifloxacin 300–600 mg [5], thus allowing for once-daily dosing, and penetrates extensively into the target tissues.

Lung tissue concentrations exceed those in plasma or serum, and the drug persists in the lung tissue for 24 h [4]. Actually, the concentrations of ulifloxacin observed 2 and 24 h after single administrations of prulifloxacin 600 mg in patients with lung cancer undergoing pneumonectomy/lobectomy were 1.24 and 0.48 μg/g, respectively. Ulifloxacin lung/plasma concentration ratios increased in time, and 2, 12 and 24 h after administration, the active compound concentrations in lung tissue were approximately 2-, 3- and 5-fold, respectively greater than the corresponding plasma concentrations (Fig. 1) [4].

Microbiological and pharmacokinetic data suggest prulifloxacin as a promising therapeutic option in the treatment of AECB. The efficacy of an antibiotic in treating AECB depends on the tissue concentration levels and the retention times in the pulmonary sites of infection [7]. Same as all fluoroquinolones, prulifloxacin produces concentration-dependent kills over a 24-h period. The pharmacodynamic parameters that correlate with clinically and microbiologically successful outcomes and prevent the emergence of bacterial resistance to fluoroquinolones are the ratio between antibiotic maximum serum concentration (C_{max}) and MIC (C_{max}/MIC) and the ratio between the area under the serum concentration-time curve during a 24-h dosing period ($AUC_{0–24}$) and MIC value ($AUC_{0–24}$/MIC) [8]. Scaglione et al. [9] have documented that the AUC/MIC ratio best correlates with efficacy against pneumococci and that the effect of the peak/MIC ratio found in some studies may be partly explained by a concentration-dependent protein binding. In vivo, ≈45% of ulifloxacin is bound to serum proteins [4], and this seems to be a real advantage in the treatment of AECB. In addition, the high and prolonged ulifloxacin lung tissue concentrations cause not only a higher C_{max}/MIC ratio, but also a more favourable AUC/MIC ratio.

Therefore, the high rate of efficacy observed in patients with AECB treated with prulifloxacin is not surprising.

Three comparative clinical trials were performed to verify the clinical and microbiological efficacy of prulifloxacin in the treatment of patients with AECB.

The enrolled patients were suffering from AECB, defined as a history of excessive tracheobronchial mucus production sufficient to cause cough and sputum production for no less than 3 months a year and for more than two consecutive years, and characterized by at least two of the following symptoms and signs: increased cough and/or dyspnoea, increased sputum volume, increased sputum purulence [10]. All patients had to have FEV_1 and FVC

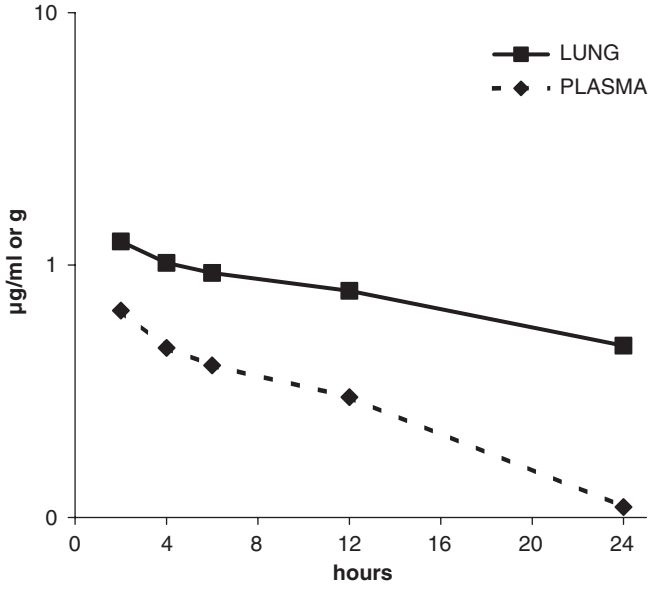

Fig. 1. Penetration of prulifloxacin (600 mg) into lung tissue after oral administration to subjects undergoing lobectomy or pneumonectomy. Points: mean values of five patients.

$\leqslant$70% predicted, Tiffenau index $\leqslant$70% and FEV_1 <80% after inhalation of salbutamol. Chest radiography had to be negative in order to rule out pneumonia. Other exclusion criteria included concurrent infections, recent antibacterial therapy, or significant hepatic or renal impairment.

In all of the studies, the patients were treated for 10 days and evaluated at baseline, on day 5–7 and day 10–12. A further evaluation was performed at the follow-up visit.

The primary efficacy parameter was the clinical evaluation at the end of treatment visit. The clinical efficacy was assessed considering fever and intensity of symptoms and signs rated by 4-point scores, namely cough (0 = absent; 1 = mild: reported in the morning only, 2 = moderate: reported night and day, but not disturbing sleep; 3 = severe: disturbing sleep), dyspnoea (0 = absent; 1 = mild; 2 = under stress; 3 = at rest), appearance of sputum (0 = clear/watery; 1 = mucoid; 2 = mucopurulent; 3 = purulent) and 24 h sputum volume (0 = none; 1 = less than 30 ml; 2 = 30–100 ml; 3 = more than 100 ml). The expected cure rate was expressed as: (i) clinical cure (resolution of all baseline symptoms and signs), (ii) clinical improvement (improvement in dyspnoea, reduction in cough and 24 h sputum volume or appearance, and fever $\leqslant$37.5 °C), (iii) failure (lack of any resolution in the magnitude of the baseline symptoms and signs). Cases reported as cured and improved at the end of treatment visit were considered successful for statistical purposes.

The microbiological response was based on the sputum sample collected at baseline and, when available, on day 10–12. A Gram stain of the sputum sample (containing $\leqslant$10 epithelial cells and >25 leukocytes per low-power field) was used to determine that the specimen was adequate for microbiological evaluation. The bacteriological response assessment was based on the following definitions: (i) eradication (original causative pathogen(s) not present after treatment or detected in concentration $\leqslant 10^4$ cfu/ml); (ii) persistence (the original pathogen(s) was/were still observed at the end-point in concentrations $>10^4$ cfu/ml); (iii) superinfection (new pathogen isolated at the end-point in concentrations $>10^4$ cfu/ml regardless of presence of the original pathogen(s). The assessment of eradication at the end of treatment visit was considered a microbiological success. Patients showing a worsening in the chronic bronchitis at the follow-up visit, underwent a microbiological examination. The microbiological responses were defined as: (i) eradication (i.e. the original causative pathogen(s) disappeared at the end-point, was/were still absent or present in concentrations $\leqslant 10^4$ cfu/ml); (ii) eradication with relapse (i.e. the original causative pathogen(s) disappeared at the end-point, reappeared in concentrations $>10^4$ cfu/ml); (iii) eradication with reinfection (i.e. the original causative pathogen(s) disappeared at the end-point, was/were not present but a new pathogen had been found in concentrations $>10^4$ cfu/ml).

3. A dose-ranging study of prulifloxacin in the treatment of AECB

The prulifloxacin dosage showing the best risk/benefit ratio in patients with AECB, was chosen based on the results of a multicentre study, where four prulifloxacin doses (300 mg once daily, 450 mg once daily, 600 mg once daily, 300 mg twice daily) were tested and compared with ciprofloxacin 500 mg twice daily [11]. The treatments were administered for 10 days. Primary objective of the study was to verify what prulifloxacin dosage showed an 80% clinical efficacy with an accuracy estimation of 15%. Secondary objectives were comparisons of clinical and microbiological efficacy between doses, and evaluation of safety and tolerability.

3.1. Patients and methods

One hundred forty-six patients (96 males, 50 females) with acute exacerbation of chronic bronchitis were enrolled. At baseline, no significant differences were found between treatment groups for severity of disease.

A total of 141 pre-treatment pathogens were isolated from the sputum of 136 patients in the intention-to-treat population. Five patients had a multibacterial infection with two strains. The most common isolates were *Enterobacteriaceae* (56), mainly *Escherichia coli* and *Klebsiella pneumoniae*, followed by *Haemophilus* spp (40), *Moraxella catarrhalis* (9) *Staphylococcus* spp (9), and *Streptococcus* spp (9). These commonly isolated pathogens appeared to be similarly distributed among the treatment groups. The high relative incidence of Gram-negative enterobacteriae detected in this trial may be related to the oral contamination of the sample, or associated with a more severe exacerbation, or to a more advanced lung disease, as the expression of a deterioration in the host defenses at the bronchial mucosa level [12,13].

3.2. Results

The percentages of clinical success were: (i) 57% (95% CI: 39–75) in the 300 mg group, (ii) 93% (95% CI: 83–100) in the 450 mg group, (iii) 100% in the 600 mg group, (iv) 90% (95% CI: 79–100) in the 300 mg twice daily group, and (v) 100% in the ciprofloxacin 500 mg twice daily group (Fig. 2). The intention-to-treat analysis showed the same results, except for the ciprofloxacin group, where the percentage of efficacy was 97% (95% CI: 91–100). The statistical analysis showed a significant global difference ($p = 0.0001$) between groups. Multiple comparisons versus the control group (ciprofloxacin) showed that only the 300 mg once-daily group was significantly different from ciprofloxacin ($p = 0.0004$). This difference clearly indicates the insufficient efficacy of the prulifloxacin 300 mg once-daily dosage. The Mantel–Haenszel test showed a significant linear trend between the daily doses of prulifloxacin 300, 450, and 600 mg ($p = 0.001$).

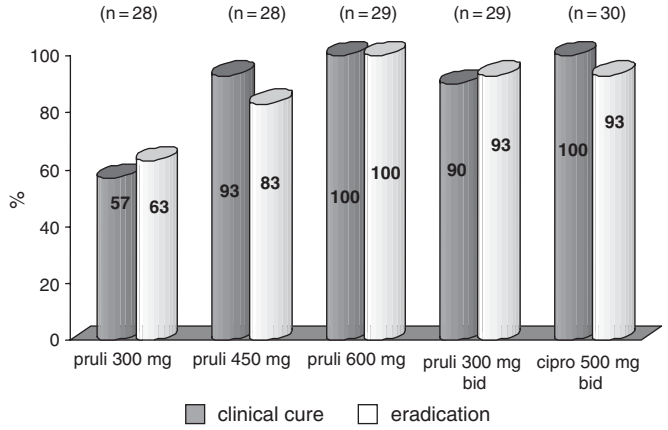

Fig. 2. Prulifloxacin: choice of dosage in the treatment of patients suffering from AECB.

At the end of treatment visit, sputum samples were not available in 62 out of 134 patients (46.2%) with positive baseline microbiological evaluation, and consequently, those cases were evaluated as "presumed microbiological eradication". Fifty-four patients (40.2%) had a sterile sputum sample, while 19 strains were still present in 18 patients, mainly in the group treated with prulifloxacin 300 mg once daily. The most common isolates were *Enterobacteriaceae* (6), *Pseudomonas* spp (3), and *Streptococcus* spp (2). The rates of success were as follows: (i) 63% in the 300 mg group, (ii) 83% in the 450 mg group, (iii) 100% in the 600 mg group, (iv) 93% in the 300 mg twice-daily group, and (v) 93% in the ciprofloxacin group (Fig. 2). No new species had appeared compared to baseline. At visit 4, the microbiological sample was collected in 18 patients only, and showed sterile in 7 of them. According to the microbiological evaluation criteria, the percentages of success compared to baseline were: (i) 78% in the 300 mg group, (ii) 91% in the 450 mg group, (iii) 100% in the 600 mg group, (iv) 93% in the 300 mg twice-daily group, and (v) 96% in the ciprofloxacin group. No cases of eradication with relapse or reinfection were found.

No serious adverse events were reported. Eighteen adverse events occurred in 11 patients (7.5%), 15 of mild and 3 of moderate intensity. The reported drug-related treatment-emergent adverse events were gastritis (7 in the 300 mg group, 4 in the 450 mg group, 1 in the 300 mg twice-daily group, and 2 in the ciprofloxacin group), flatulence (2 in the 300 mg group), headache (1 in the 300 mg twice-daily group). None of the events required discontinuation of therapy and all symptoms disappeared spontaneously.

3.3. Conclusions

The results of this trial show that prulifloxacin is effective and safe, particularly at the dosage of 600 mg once daily that is comparable to ciprofloxacin 500 mg twice daily, a standard reference widely used in treating AECB. The statistical analyses show a significant linear trend between the doses of prulifloxacin 300, 450, and 600 mg, which would appear to indicate an interesting relationship between doses employed and responses obtained. It is for this reason that the 600 mg once-daily dose was selected for use in the pivotal clinical trials.

4. Evaluation of efficacy and tolerability of prulifloxacin versus ciprofloxacin in the treatment of AECB

The comparative efficacy of prulifloxacin 600 mg once daily and ciprofloxacin 500 mg twice daily, both administered for 10 days, was evaluated in a multicentre, double-blind, double-dummy study [14].

4.1. Patients and methods

Two hundred thirty-five patients (179 males, 56 females) with AECB were enrolled in the trial. One hundred seventeen patients were randomized to receive prulifloxacin, and 118 ciprofloxacin (Fig. 3).

Patients who withdrew from the study for lack of efficacy reasons or treatment-related adverse effects were considered treatment failures. Patients who were cured or improved at the end of treatment visit were re-evaluated at the follow-up in order to determine the relapse rate.

A total of 173 pre-treatment pathogens were isolated from 144 patients. The most common isolates were *H. influenzae* (22.5%), *S. pneumoniae* (12.1%) and *K. pneumoniae* (7.5%). These commonly isolated pathogens appeared to be similarly distributed in the two treatment groups. All the pre-treatment isolates, with the exception of 18 organisms from 16 patients, were susceptible to both prulifloxacin and ciprofloxacin.

4.2. Results

Of the 235 patients enrolled, 219 (93%) completed the study. Sixteen patients (8 in the prulifloxacin and 8 in

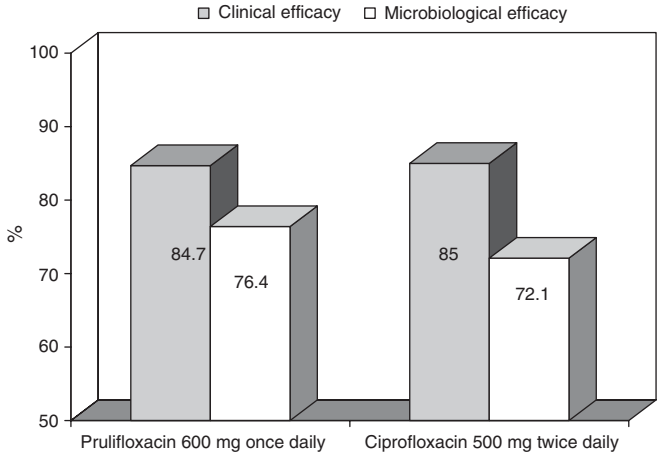

Fig. 3. Results of phase III studies: prulifloxacin 600 mg once daily versus ciprofloxacin 500 mg twice daily (235 patients).

the ciprofloxacin group) withdrew prematurely. The efficacy analysis was performed using the modified intention-to-treat (MITT) population, which consisted of 219 patients that completed the study plus 5 patients who withdrew for treatment-related adverse events or lack of efficacy.

The therapeutic success rates at the end of treatment visit were similar between prulifloxacin and ciprofloxacin, being 84.7% (95% CI: 78.0, 91.4) versus 85.0% (95% CI: 78.4, 91.5) (Fig. 3). Prulifloxacin was statistically non-inferior to ciprofloxacin. One hundred eighty-four patients (91 in the prulifloxacin group and 93 in the ciprofloxacin group) returned for the follow-up visit and were re-evaluated in order to determine the frequency of relapses. Two out of 91 and 1 out of 93 patients presented a new episode of AECB.

The bacteriological evaluation was performed in 133 patients who had presented bacterial strains at baseline. Nineteen patients (14 prulifloxacin- and 5 ciprofloxacin-treated patients) out of 133 were assessed as showing presumed microbiological eradication since they had recovered and no adequate sputum had been produced. Microbiological eradication occurred in 41/72 patients for prulifloxacin and 39/61 in the ciprofloxacin group. Fourty-seven pathogens were detected in 34 patients (20 cases of persistence and 27 of superinfection). At the end of the treatment, the bacteriological success rate for the microbiologically evaluable patients was 76.4% (95% CI: 66.6–86.2) for the group receiving prulifloxacin, and 72.1% (95% CI: 60.9–83.4) for the group receiving ciprofloxacin. There was equivalence between groups receiving prulifloxacin and ciprofloxacin (95% CI: −8.27%). At visit 4, 3/133 patients still presented bacterial strains, 2 patients (one persistence, one superinfection) in the prulifloxacin group and one patient (persistence) in the ciprofloxacin group.

Both treatment regimens were well tolerated. The most frequently reported drug-related treatment-emergent adverse events were gastric pain, nausea, diarrhoea, dyspepsia and pruritus. No unexpected laboratory findings were observed. Overall, 2 patients dropped out for drug-related adverse events: one in the prulifloxacin group because of mild pruritus and moderate gastric pain, and the other in the ciprofloxacin group because of fever, diarrhoea and vomiting. The concomitant administration of prulifloxacin or ciprofloxacin and theophylline appeared to be well tolerated in the 47 patients (22 prulifloxacin and 25 ciprofloxacin) who received both drugs.

4.3. Conclusions

The results of this study indicate that 10-day courses of prulifloxacin 600 mg once daily are as effective as ciprofloxacin 500 mg twice daily in the treatment of AECB. Interestingly, although fluoroquinolones are generally not considered the first choice treatment for infections caused by *S. pneumoniae*, data emerging from this clinical trial evidenced a satisfactory microbiological efficacy of prulifloxacin against *S. pneumoniae* (8/9, 88.9% eradication), which is slightly higher compared to the results obtained with the reference medication (9/12, 75% eradication).

5. Evaluation of efficacy and tolerability of prulifloxacin versus co-amoxiclav in the treatment of AECB

Co-amoxiclav is frequently and appropriately prescribed in patients with AECB, given the high incidence of *H. influenzae* [15] and the increasing ß-lactam resistance (via ß-lactamase production) among such isolates [16]. However, *S. pneumoniae* is frequently implicated in AECB too, with resistance to ß-lactams increasing at an alarming rate [15,17]. Since the resistance mechanism involves alteration of penicillin-binding proteins, isolates of *S. pneumoniae* with reduced susceptibility to penicillin also show decreased susceptibility to co-amoxiclav [18]. The utility of alternative antimicrobials is also being hampered by the emergence of drug-resistant strains.

In this multicentre double-blind, double-dummy study, co-amoxiclav at the recommended dosage of 1 g twice daily was chosen as the reference treatment in view of its proven efficacy in the first-line empiric treatment of respiratory infections such as AECB [19].

5.1. Patients and methods

Two hundred fourteen (117 males, 97 females) adult patients with an acute episode of chronic bronchitis exacerbation were enrolled. As regards distribution, no significant differences in sex, age, height, weight or vital signs were found at baseline between groups. One hundred fifty-five bacterial strains were identified in 152 patients. Although the broncho-pulmonary origin of the sputum sample was verified through Bartlett's score, oral contamination occurred. Excluding strains clearly due to contamination, the most common isolates were *E. coli* (26), *K. pneumoniae* (20), *H. influenzae* (14) and *S. pneumoniae* (12). Once again, Gram-negative enterobacteriae showed slightly prevailing.

5.2. Results

At the end of treatment, therapeutic success rates were similar between prulifloxacin and co-amoxiclav, being 92.5% (95% CI 87.4, 97.5) versus 93.4% (95% CI 88.6, 98.1) (Fig. 4). Statistical analyses demonstrated the therapeutic equivalence of prulifloxacin and co-amoxiclav (lower limit of the one-tailed 95% CI−6.7%). Two weeks after completing the treatment, two patients in the prulifloxacin group and one in the co-amoxiclav group presented an exacerbation of chronic bronchitis.

Microbiological success was documented at the end of treatment in 94.9% (95% CI 90.0, 99.8) of the prulifloxacin

and 93.1% (95% CI 87.3, 99.0) of the co-amoxiclav recipients. Persistences or superinfentions were observed in 13 patients showing 16 strains. At the follow-up, one persistence was reported in the prulifloxacin group, while no eradications with relapse or reinfections were observed.

Two patients dropped out due to drug-related adverse events: one in the prulifloxacin group because of moderate skin rush, and the other in the co-amoxiclav group because of moderate gastric pain and moderate diarrhoea. In both groups the most frequent treatment related adverse event was gastric pain (6.5% in the prulifloxacin group and 11.4% in the co-amoxiclav group).

5.3. Conclusions

The present study upholds the use of prulifloxacin 600 mg once-daily dosage regimen as the first-line treatment for AECB, because of its proven efficacy and favourable safety profile. Results show that prulifloxacin once daily is at least as effective and well tolerated as co-amoxiclav 1 g twice daily. This should be considered an advantage in clinical practice because its once-daily dosing regimen may favour the patients' compliance.

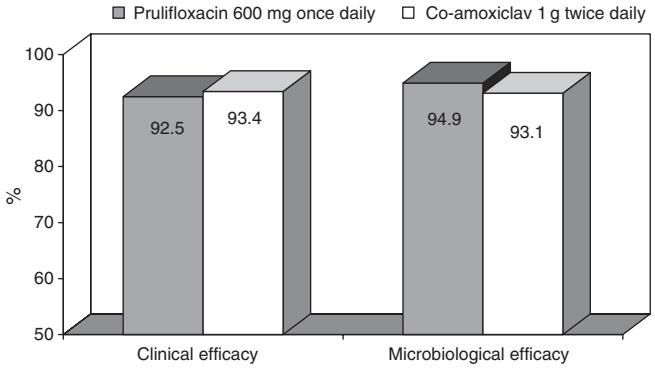

Fig. 4. Results of phase III studies: prulifloxacin 600 mg once daily versus co-amoxiclav 1 g twice daily (214 patients).

6. Positioning of prulifloxacin in the treatment of AECB

Within AECB, the antibiotic therapy aims at resolving the acute infection and restore the patient to an infection-free state. An antimicrobial agent effective in such infections would be expected to achieve local tissue concentrations high enough to exceed MIC levels for the causative pathogens. Repeated episodes of infection combined with inadequate medical management may contribute to ongoing deterioration of the respiratory function. Two particular challenges face community prescribers: patient compliance and increasing antibiotic resistance. Compliance with treatment is a concern, particularly as it has been previously shown that compliance cannot be predicted accurately from patient profiles [20].

The limited bacteriological spectrum of the existing agents, coupled in some instances with the need for multiple daily dosing (which can lead to poor compliance) [20], highlight the need for new agents which not only are effective against the broad range of AECB likely pathogens, including resistant strains, but which also have convenient dosage regimens.

All the described findings clearly indicate that prulifloxacin is a new therapeutic prospect in the antimicrobial therapy of AECB (Fig. 5). Complicated forms which involve particular risks for patients and are generally caused by *Enterobacteriaceae*, *Pseudomonas* spp, Gram-negative or resistant microorganisms, are its main indication. At the same time, prulifloxacin's good profile of activity does not exclude its use even in simple forms, like those caused by *M. pneumoniae* or *Chlamydia pneumoniae*, but solid data supporting the activity of this agent against atypical bacteria are still lacking. Prulifloxacin is even suitable for the complicated forms caused by *H. influenzae*, *S. pneumoniae*, Gram-positive cocci, and *M. catarrhalis*, although the in vitro data are not homogeneous in defining the activity of prulifloxacin against *S. pneumoniae* [21,22]. As a matter of fact, the high and long-lasting penetration of prulifloxacin into the pulmonary tissues determines the relationship between its tissue pharmacokinetics and

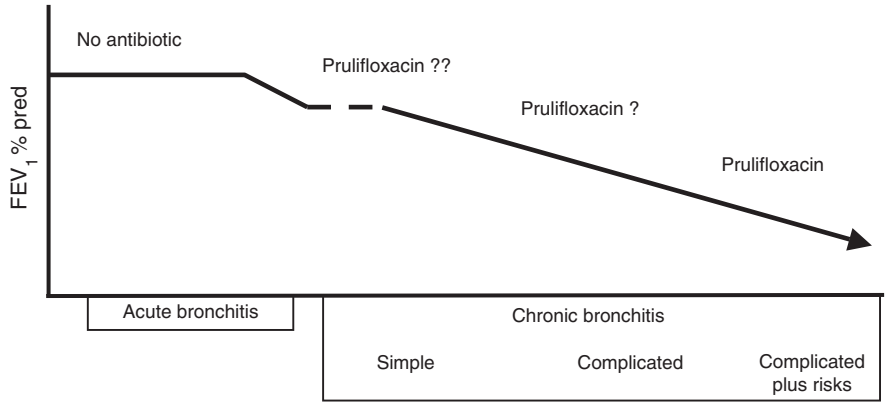

Fig. 5. Proposed role of prulifloxacin considering type of bronchitis and pulmonary function.

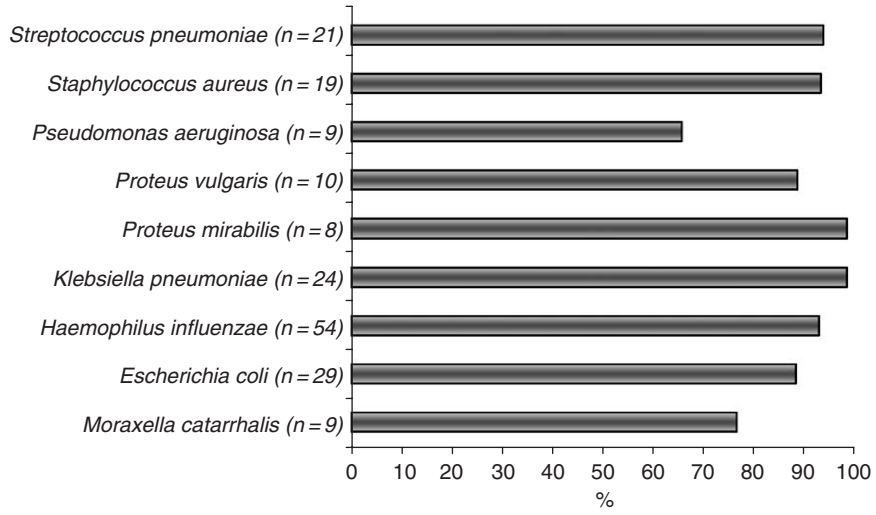

Fig. 6. Prulifloxacin 600 mg for 10 days. Bacterial eradication rates (%).

pharmacodynamics, that is quite different from that in blood. This essential difference could explain the high rate of in vivo efficacy showed by prulifloxacin against the majority of *S. pneumoniae* strains found in the sputum of patients with AECB (Fig. 6). In addition, since the good patient compliance with therapy is a key factor in the successful treatment of any infection [23], the once-daily treatment with prulifloxacin may have some compliance advantages compared to the twice-daily treatment with agents such as ciprofloxacin or co-amoxiclav.

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Further reading

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