Prulifloxacin: a new antibacterial fluoroquinolone

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In the last few years, the antimicrobial activity, efficacy and relative safety of fluoroquinolones have made them attractive for the treatment of community-acquired and nosocomial infections. Prulifloxacin is a new fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and -negative bacteria. Prulifloxacin is available for oral use, and after absorption is metabolized in to the active form, ulifloxacin. It exhibits good penetration in target tissues and a long elimination half-life, allowing once-daily administration. A number of randomized, controlled clinical trials carried out in Europe demonstrated the efficacy of prulifloxacin in the treatment of urinary tract (acute uncomplicated and complicated) and respiratory tract infections (acute exacerbations of chronic bronchitis), in comparison with the most widely used drugs such as ciprofloxacin, co-amoxiclav and pefloxacin. Prulifloxacin was generally well tolerated. The most frequent adverse reactions observed in clinical trials were gastric pain, diarrhea, nausea and skin rash. This review focuses on the characteristics of prulifloxacin, summarizing the relevant preclinical and clinical data.

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Quinolones constitute a large class of synthetic antimicrobial agents that are highly effective in the treatment of many types of infectious diseases. The primary target of quinolones are Type II DNA topoisomerases, enzymes which induce DNA topological changes in order to allow transcription, replication, recombination and repair. When the topoisomerases' physiological function is blocked, DNA replication is inhibited and followed by bacterial cell death [1–3].

The first quinolone was nalidixic acid, a quinine derivative obtained as an impurity during manufacturing of that drug [4]. From the core structure of nalidixic acid (naphthyridone), two types of products have been synthesized, naphthyridones and quinolones, basically differing at the 8-position atom: nitrogen or carbon, respectively. However, the generic name of quinolones is usually employed for both groups of pharmacore molecules.

First-generation quinolones were only useful for the treatment of urinary tract infections (UTIs) due to a limited spectrum of antibacterial activity, irregular absorption and low tissular distribution. The addition of a fluorine atom at the 6-position (fluoroquinolones), followed by the addition of a piperazine group at C-7 improved the potency and oral absorption of these drugs [5,6].

Later, many quinolone properties, and particularly their activity spectrum, were improved by the addition of different substituents at the N-1, C-2, C-5 and C-7 positions. Currently, new fluoroquinolones have a broad *in vitro* spectrum, which includes Enterobacteriaceae, *Haemophilus*, *Pseudomonas* and other Gram-negative bacilli, *Legionella*, *Mycoplasma*, *Chlamydia*, Gram-positive cocci (including staphylococci and *Streptococcus pneumoniae*) and anaerobic bacteria [5–7].

These compounds have now been used in clinical practice for over 10 years, and during this time, an increased understanding of structure–function relationships of the fluoroquinolones has led to the development of better compounds in terms of both the spectrum of antimicrobial cover and improved pharmacokinetics, allowing a once-daily dosing and use as monotherapy [5,6,8].

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However, the use of these new compounds has been limited by some adverse events inherent to the class or due to structural modifications [9].

The most common adverse events associated with quinolones involve the gastrointestinal tract (nausea and diarrhea) and the CNS, and have been chiefly reported in elderly people treated with high doses [9].

Phototoxicity is a dermatological complication commonly associated with specific quinolones, particularly lomefloxacin, sitafloxacin and sparfloxacin, and is strictly related to the chemical structure. It is determined by the nature of the 8-position substituent, with halogen causing the greatest photo reaction, while hydrogen and methoxy show little light-induced toxicity [9,10]. Although sometimes considered a class effect, cardiac toxicity and, in particular, the potential to prolong the QTc interval has been associated principally with grepafloxacin and sparfloxacin [9,11].

Allergic reactions are rare. Arthropathies and tendonitis, in particular an increased risk of Achilles tendon rupture after exposure to quinolones, have been reported [12]. Although cartilage erosions have been observed in experimental models, such lesions have not been clinically observed. Administration of quinolones is not recommended in children or pregnant females; however, the use of ciprofloxacin for some indications in children has been recently approved by the US Food and Drug Administration (FDA) [9].

The acquired bacterial resistance to quinolones may be mediated by three different mechanisms: chromosomal mutations that alter the target enzymes DNA gyrase and topoisomerase IV or activate the efflux systems that pump the drug out of the cytoplasm. Transferable plasmid-mediated quinolone resistance in Europe has recently been reported [13–15]. The simultaneous combination of different mechanisms of resistance can occur in highly resistant clinical isolated bacteria [16].

Prulifloxacin is the prodrug of ulifloxacin. After oral administration, prulifloxacin is rapidly and extensively transformed into the active metabolite ulifloxacin [17,18], a fluoroquinolone with a broad spectrum of activity against Gram-negative bacteria and some Gram-positive cocci. As with other fluoroquinolones, ulifloxacin prevents bacterial DNA transcription, replication, repair and recombination through inhibition of bacterial DNA gyrases and topoisomerase IV enzymes.

Chemistry

Prulifloxacin (NM441; AF 3012; CAS 123447–62–1) or *R,S*-6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid, is a lipophilic prodrug which, following oral administration, is rapidly absorbed and hydrolyzed to the active compound *R,S*-6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid – ulifloxacin (NM394; AF 3013; CAS 112984–60–8) (FIGURE 1) [19,20].

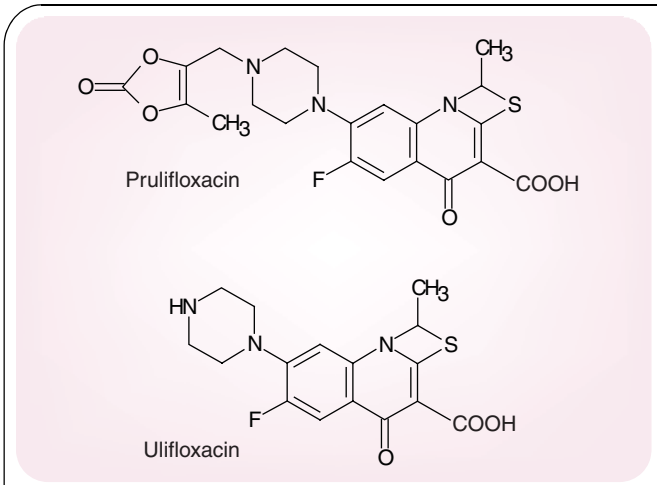

Figure 1. Prulifloxacin and ulifloxacin. Prulifloxacin: *R,S*-6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid. Ulifloxacin: *R,S*-6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid.

Mechanism of action

Quinolones have a unique mechanism of action and are bactericidal agents. Their primary target are the bacterial enzymes DNA gyrase and DNA topoisomerase IV, essential for DNA replication. Both are large, complex enzymes composed of two pairs of subunits. The subunits of DNA gyrase are the GyrA and GyrB proteins, encoded respectively by the *gyr*A and *gyr*B genes. The corresponding subunits of topoisomerase IV are ParC and ParE, encoded respectively by the *parC* and *parE* genes. The two enzymes work together in the replication, transcription, recombination and repair of DNA. A few bacteria are able to function with DNA gyrase alone, but most bacteria have both enzymes. Quinolones block the reaction and trap gyrase or topoisomerase IV as a drug–enzyme–DNA complex, with a subsequent release of lethal, double-stranded DNA breaks [21].

In Gram-negative bacteria, gyrase is more susceptible to inhibition by quinolones than topoisomerase IV, whereas, in Gram-positive bacteria, topoisomerase IV is usually the main target, and gyrase is intrinsically less susceptible.

In vitro studies demonstrate that the minimum inhibitory concentration (MIC) of quinolones are determined by the inhibitory activity against the preferential target, DNA gyrase or topoisomerase IV [1,21–26].

Experimental data evaluating the inhibitory concentration (IC_{50}) of several quinolones on DNA gyrase and topoisomerase IV from *Pseudomonas aeruginosa*, showed that the activity of ulifloxacin (1.21 and 21.1 µg/ml, respectively) and ciprofloxacin (1.17 and 23.6 µg/ml) are similar and better than those of levofloxacin (1.46 and 35.3 µg/ml) and gatifloxacin (2.21 and 46.4 µg/ml) [27].

This finding has been confirmed using purified DNA gyrases from different microorganisms. The ulifloxacin IC_{50} values for *Staphylococcus aureus*, *Escherichia coli* and *P. aeruginosa* purified

DNA gyrases were 18.0, 0.41 and 2.05 µg/ml, respectively. These results were comparable with or better than those obtained with reference drugs [28].

Antimicrobial spectrum

As reported in several studies, ulifloxacin has a broad spectrum of activity against most Gram-negative and some Gram-positive strains frequently involved in respiratory infections and UTIs [19,20,28–30].

The core MIC data shown in the present review has been selected from a study that compares the *in vitro* activity of ulifloxacin, ciprofloxacin, moxifloxacin, trovafloxacin, grepafloxacin and levofloxacin against 537 clinical isolates from Spain [29]. Activity was assessed by a twofold agar dilution procedure, according to the Clinical and Laboratory Standards Institute (CLSI)/National Commmittee for Clinical Laboratory Standards (NCCLS) guidelines [31]. The breakpoints for ulifloxacin are less than or equal to 1, 2 and greater than or equal to 4 µg/ml for susceptible, intermediate and resistant strains, respectively [19,32]. The MIC_{50} and MIC_{90} and MIC ranges of ulifloxacin and reference drugs against Gram-negative clinical isolates are reported in TABLE 1, and those against Gram-positive bacteria in TABLE 2 [29].

Gram-negative bacteria

Against Enterobacteriaceae, ulifloxacin is the most active quinolone when compared with ciprofloxacin, moxifloxacin, trovafloxacin, grepafloxacin and levofloxacin, with MIC_{90} values ranging from less than or equal to 0.015–0.25 µg/ml. Ulifloxacin MIC values for nalidixic acid-susceptible enterobacteria were comparable with or slightly lower than those of ciprofloxacin for most species. Enteropathogenic enterobacteria was shown to be very susceptible to all quinolones tested; ulifloxacin and ciprofloxacin were the most active drugs against enteropathogenic strains of *E. coli*, *Shigella* (MIC_{90} ≤ 0.015 µg/ml) and *Salmonella enterica* (MIC_{90} 0.03 µg/ml) (TABLE 1). These results are similar to those published by Ozaki and colleagues [20], Yoshida and colleagues [28] and Montanari and colleagues [30].

Ulifloxacin and ciprofloxacin are the quinolones with the most potent activity against *P. aeruginosa* (MIC_{90} 1 µg/ml), followed by levofloxacin and trovafloxacin (MIC_{90} 2 µg/ml) [29].

Against the other Gram-negative bacteria tested in the study (*Haemophilus influenzae* and *Moraxella catarrhalis*), all tested quinolones where shown to be highly active with MIC_{90} ranging from less than or equal to 0.015–0.06 µg/ml for *H. influenzae* and from 0.06 to 0.12 µg/ml for *M. catarrhalis.*

Ulifloxacin had the lowest MIC against *H. influenzae* and inhibited all the strains at concentrations lower than 0.015 µg/ml. Against *M. catarrhalis,* ulifloxacin activity was comparable with trovafloxacin and grepafloxacin (MIC_{90} 0.06 µg/ml).

Ulifloxacin and moxifloxacin with MIC_{90} of 1 µg/ml were active, but less potent than the other quinolones against 14 strains of *Legionella pneumophila*.

Bacterial strains with acquired resistance to nalidixic acid (*E. coli* Nal^R, *Klebsiella pneumoniae* Nal^R *and Proteus mirabilis* Nal^R) and ciprofloxacin-resistant *P. aeruginosa* Cip^R were also tested for their susceptibility to quinolones. *E. coli* Nal^R and *K. pneumoniae* Nal^R strains remain susceptible to ulifloxacin and to the other fluoroquinolones, despite the increase in MIC values: MIC_{90} of ulifloxacin against *E. coli* Nal^R strains increased up to 1 µg/ml and against *K. pneumoniae* Nal^R strains up to 0.25 µg/ml. On the contrary, all *P. mirabilis* Nal^R strains were resistant to all tested quinolones, with MIC_{90} values greater than or equal to 4 µg/ml.

A total of 75 strains of *P. aeruginosa* were susceptible to ulifloxacin and ciprofloxacin with MIC_{90} of 1 µg/ml; however, 30 strains of *P. aeruginosa* that were resistant to ciprofloxacin presented cross resistance for all the other fluoroquinolones.

Gram-positive bacteria

In vitro studies show that ulifloxacin, ciprofloxacin and levofloxacin are less potent than trovafloxacin and grepafloxacin against Gram-positive pathogens [29]. MIC_{90} values of ulifloxacin against *S. pyogenes*, *S. agalactiae* and methicillin-susceptible *S. aureus* ranged from 0.25 to 1 µg/ml, and all strains tested were susceptible to ulifloxacin (TABLE 2). No activity was detected for all quinolones against methicillin-resistant *S. aureus* strains.

In this study, ulifloxacin activity against *S. pneumoniae* was low and ranged from 0.12 to greater than 4 µg/ml, with a MIC_{50} of 2 µg/ml and a MIC_{90} greater than 4 µg/ml. The other quinolones showed higher activity. Similar results are reported by Ozaki and colleagues [20] and Yoshida and colleagues [28], while in an *in vitro* study that includes 36 *S. pneumoniae* community isolates from Italy, Montanari and colleagues found a higher susceptibility to ulifloxacin with a MIC range from less than or equal to 0.015–2 µg/ml and MIC_{90} of 1 µg/ml [30]. Saito and colleagues have calculated and proposed MIC values of 2 µg/ml as clinical breakpoints for prulifloxacin in pulmonary infections, after 200 or 500 mg oral doses [33].

The MIC values of ulifloxacin against vancomycin-susceptibile enterococci were higher than those against the other Gram-positive cocci, with ranges of 0.5–4 and 1–4 µg/ml against *Enterococcus faecalis* and *Enterococcus faecium*, respectively.

Pharmacokinetics

The pharmacokinetic properties of prulifloxacin were investigated in experimental animal models [34]. After oral administration in rats, the drug was mainly absorbed in the upper small intestine and quantitatively metabolized by esterases to the active metabolite ulifloxacin in the portal blood and in the liver, before entering the systemic circulation [18].

The maximum tissue distribution in rats was obtained 1 h after oral administration, with concentrations high in the liver and kidneys, moderate in the spleen, pancreas and lung, and negligible in the cerebrum and cerebellum [34]. In lactating rats, the metabolite concentration in milk was higher than in plasma [35].

Table 1. Antibacterial activity of ulifloxacin and other quinolones against Gram-negative bacterial strains [29].

Organisms (no. of strains)	Antimicrobial agent	MIC (μg/ml)		
		Range	*50%*	*90%*
Escherichia coli (11)	Ulifloxacin	≤0.015–0.03	≤0.015	≤0.015
	Nalidixic acid	2–>4	4	4
	Ciprofloxacin	≤0.015	≤0.015	≤0.015
	Moxifloxacin	0.03–0.5	0.06	0.12
	Trovafloxacin	≤0.015–0.06	0.03	0.06
	Grepafloxacin	0.03–0.25	0.03	0.12
	Levofloxacin	0.03–0.12	0.03	0.06
E. coli Nal^R (15)	Ulifloxacin	0.12–1	0.12	1
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	0.25–1	0.25	1
	Moxifloxacin	0.5–4	1	2
	Trovafloxacin	0.25–4	0.5	1
	Grepafloxacin	0.5–>4	2	2
	Levofloxacin	0.5–2	1	2
E. coli enterohaemorragic (10)	Ulifloxacin	≤0.015–0.5	≤0.015	≤0.015
	Nalidixic acid	1->32	2	2
	Ciprofloxacin	≤0.015–2	0.03	0.03
	Moxifloxacin	0.06–2	0.06	0.06
	Trovafloxacin	0.03–4	0.06	0.06
	Grepafloxacin	0.03–4	0.06	0.06
	Levofloxacin	0.5–2	0.5	0.5
E. coli enterotoxigenic (12)	Ulifloxacin	≤0.015–1	≤0.015	≤0.015
	Nalidixic acid	1–4	2	2
	Ciprofloxacin	≤0.015	0.03	0.03
	Moxifloxacin	0.03–0.5	0.06	0.12
	Trovafloxacin	≤0.015–0.12	0.06	0.06
	Grepafloxacin	≤0.015–0.5	0.06	0.06
	Levofloxacin	0.03–0.12	0.5	0.5
Klebsiella pneumoniae (9)	Ulifloxacin	≤0.015–0.12	0.03	0.12
	Nalidixic acid	2–>4	4	8
	Ciprofloxacin	≤0.015–0.25	0.03	0.25
	Moxifloxacin	0.06–1	0.12	1
	Trovafloxacin	0.03–0.5	0.12	0.5
	Grepafloxacin	0.03–0.5	0.12	0.5
	Levofloxacin	0.06–1	0.06	1

Cip^R: Ciprofloxacin resistant; Cip^S: Ciprofloxacin susceptible; MIC: Minimum inhibitory concentration; Nal^R: Nalidixic acid resistant.

Table 1. Antibacterial activity of ulifloxacin and other quinolones against Gram-negative bacterial strains [29] (cont.).

Organisms (no. of strains)	Antimicrobial agent	MIC (μg/ml)		
		Range	*50%*	*90%*
K. pneumoniae Nal^R (14)	Ulifloxacin	0.06–1	0.25	0.25
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	0.12–1	0.25	1
	Moxifloxacin	0.25–4	1	2
	Trovafloxacin	0.06–2	0.5	2
	Grepafloxacin	0.25–4	1	2
	Levofloxacin	0.25–2	1	1
Klebsiella oxytoca (10)	Ulifloxacin	≤0.015–0.03	≤0.015	0.03
	Nalidixic acid	2–8	2	8
	Ciprofloxacin	≤0.015–0.03	≤0.015	0.03
	Moxifloxacin	0.12–0.25	0.12	0.25
	Trovafloxacin	0.03–0.12	0.12	0.12
	Grepafloxacin	0.06–0.12	0.12	0.12
	Levofloxacin	0.06–0.12	0.06	0.06
Proteus mirabilis (10)	Ulifloxacin	≤0.015	≤0.015	≤0.015
	Nalidixic acid	4–8	4	8
	Ciprofloxacin	≤0.015–0.03	0.03	0.03
	Moxifloxacin	0.25–1	0.25	0.5
	Trovafloxacin	0.25–0.5	0.25	0.5
	Grepafloxacin	0.25–1	0.25	0.5
	Levofloxacin	0.06–0.25	0.06	0.12
P. mirabilis Nal^R (12)	Ulifloxacin	0.06–>4	1	>4
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	0.5–>4	>4	>4
	Moxifloxacin	1–>4	>4	>4
	Trovafloxacin	0.5–>4	>4	>4
	Grepafloxacin	2–>4	>4	>4
	Levofloxacin	0.25– >4	4	>4
Proteus vulgaris (10)	Ulifloxacin	≤0.015	≤0.015	≤0.015
	Nalidixic acid	2–4	4	4
	Ciprofloxacin	≤0.015–0.03	0.03	0.03
	Moxifloxacin	0.25–0.5	0.25	0.5
	Trovafloxacin	0.12–0.5	0.12	0.5
	Grepafloxacin	0.12–0.5	0.25	0.5
	Levofloxacin	0.06	0.06	0.06

Cip^R: Ciprofloxacin resistant; Cip^S: Ciprofloxacin susceptible; MIC: Minimum inhibitory concentration; Nal^R: Nalidixic acid resistant.

Table 1. Antibacterial activity of ulifloxacin and other quinolones against Gram-negative bacterial strains [29] (cont.).

Organisms (no. of strains)	Antimicrobial agent	MIC (μg/ml)		
		Range	*50%*	*90%*
Providencia rettgeri (6)	Ulifloxacin	≤0.015–1	0.03	1
	Nalidixic acid	4–>32	4	>32
	Ciprofloxacin	0.03–1	0.03	1
	Moxifloxacin	0.25–2	0.5	2
	Trovafloxacin	0.25–2	0.25	2
	Grepafloxacin	0.25–2	0.25	2
	Levofloxacin	0.06–2	0.12	2
Providencia stuartii (10)	Ulifloxacin	0.03–>4	2	>4
	Nalidixic acid	2–>32	>32	>32
	Ciprofloxacin	0.03–>4	1	>4
	Moxifloxacin	0.25–>4	2	>4
	Trovafloxacin	0.12–>4	2	>4
	Grepafloxacin	0.12–>4	1	>4
	Levofloxacin	0.12–>4	1	>4
Morganella morganii (11)	Ulifloxacin	≤0.015–0.06	≤0.015	0.03
	Nalidixic acid	1–>32	2	4
	Ciprofloxacin	≤0.015–0.06	≤0.015	0.03
	Moxifloxacin	0.06–0.5	0.12	0.5
	Trovafloxacin	0.12–1	0.12	0.5
	Grepafloxacin	0.12–1	0.12	0.25
	Levofloxacin	0.03–0.25	0.03	0.12
Enterobacter aerogenes (11)	Ulifloxacin	≤0.015–1	≤0.015	0.03
	Nalidixic acid	2–32	4	4
	Ciprofloxacin	≤0.015–2	0.03	0.03
	Moxifloxacin	0.06–2	0.12	0.5
	Trovafloxacin	0.03–2	0.12	0.12
	Grepafloxacin	0.03–2	0.12	0.25
	Levofloxacin	0.03–2	0.06	0.12
Enterobacter cloacae (14)	Ulifloxacin	≤0.015–0.12	≤0.015	0.12
	Nalidixic acid	2–>32	4	>32
	Ciprofloxacin	≤0.015–0.5	≤0.015	0.12
	Moxifloxacin	≤0.015–2	0.12	0.5
	Trovafloxacin	≤0.015–1	0.06	0.5
	Grepafloxacin	≤0.015–1	0.12	0.5
	Levofloxacin	0.03–1	0.06	0.5

Cip^R: Ciprofloxacin resistant; Cip^S: Ciprofloxacin susceptible; MIC: Minimum inhibitory concentration; Nal^R: Nalidixic acid resistant.

Table 1. Antibacterial activity of ulifloxacin and other quinolones against Gram-negative bacterial strains [29] (cont.).

Organisms (no. of strains)	Antimicrobial agent	MIC (μg/ml)		
		Range	*50%*	*90%*
Serratia marcescens (11)	Ulifloxacin	≤0.015–1	0.12	0.5
	Nalidixic acid	1–32	2	8
	Ciprofloxacin	≤0.015–1	0.12	0.5
	Moxifloxacin	0.12–4	0.5	4
	Trovafloxacin	0.12–4	0.5	4
	Grepafloxacin	0.12–4	1	4
	Levofloxacin	0.03–2	0.25	2
Citrobacter freundii (12)	Ulifloxacin	≤0.015–1	≤0.015	0.25
	Nalidixic acid	4–>32	4	16
	Ciprofloxacin	≤0.015–2	0.03	0.5
	Moxifloxacin	0.12–4	0.5	4
	Trovafloxacin	0.06–4	0.12	4
	Grepafloxacin	0.06–4	0.25	4
	Levofloxacin	0.03–2	0.12	1
Citrobacter koseri (11)	Ulifloxacin	≤0.015–2	≤0.015	≤0.015
	Nalidixic acid	2–>32	4	4
	Ciprofloxacin	≤0.015–2	≤0.015	0.12
	Moxifloxacin	0.06–4	0.06	0.12
	Trovafloxacin	≤0.015–>4	0.03	0.12
	Grepafloxacin	0.03–>4	0.06	0.12
	Levofloxacin	0.03–4	0.03	0.06
Salmonella enterica (11)	Ulifloxacin	≤0.015–0.12	≤0.015	0.03
	Nalidixic acid	1–>32	4	4
	Ciprofloxacin	≤0.015–0.25	≤0.015	0,03
	Moxifloxacin	≤0.015–1	0.12	0.12
	Trovafloxacin	≤0.015–1	0.12	0.12
	Grepafloxacin	≤0.015–1	0.12	0.12
	Levofloxacin	≤0.015–0.5	0.06	0.06
Shigella sonnei (10)	Ulifloxacin	≤0.015	≤0.015	≤0.015
	Nalidixic acid	1–2	2	2
	Ciprofloxacin	≤0.015	≤0.015	≤0.015
	Moxifloxacin	0.03–0.06	0.03	0.03
	Trovafloxacin	≤0.015	≤0.015	≤0.015
	Grepafloxacin	≤0.015–0.03	0.03	0.03
	Levofloxacin	≤0.015–0.03	0.03	0.03

Cip^R: Ciprofloxacin resistant; Cip^S: Ciprofloxacin susceptible; MIC: Minimum inhibitory concentration; Nal^R: Nalidixic acid resistant.

Table 1. Antibacterial activity of ulifloxacin and other quinolones against Gram-negative bacterial strains [29] (cont.).

Organisms (no. of strains)	Antimicrobial agent	MIC (μg/ml)		
		Range	*50%*	*90%*
Shigella flexneri (10)	Ulifloxacin	≤0.015	≤0.015	≤0.015
	Nalidixic acid	1–2	1	2
	Ciprofloxacin	≤0.015	≤0.015	≤0.015
	Moxifloxacin	0.03–0.06	0.03	0.03
	Trovafloxacin	≤0.015	≤0.015	≤0.015
	Grepafloxacin	≤0.015–0.03	≤0.015	0.03
	Levofloxacin	≤0.015–0.03	0.03	0.03
Pseudomonas aeruginosa Cip^S (75)	Ulifloxacin	≤0.015–1	0.25	1
	Nalidixic acid	4–>32	>32	>32
	Ciprofloxacin	0.06–1	0.5	1
	Moxifloxacin	0.5–>4	4	>4
	Trovafloxacin	0.25–4	1	2
	Grepafloxacin	0.25–>4	1	4
	Levofloxacin	0.25–4	1	2
P. aeruginosa Cip^R (30)	Ulifloxacin	1–>4	>4	>4
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	2–>4	>4	>4
	Moxifloxacin	1–>4	>4	>4
	Trovafloxacin	2–>4	>4	>4
	Grepafloxacin	4–>4	>4	>4
	Levofloxacin	4–>4	>4	>4
Haemophilus influenzae (20)	Ulifloxacin	≤0.015	≤0.015	≤0.015
	Nalidixic acid	1–2	1	2
	Ciprofloxacin	≤0.015–0.06	≤0.015	0.03
	Moxifloxacin	≤0.015–0.03	≤0.015	0.03
	Trovafloxacin	≤0.015–0.06	0.03	0.06
	Grepafloxacin	≤0.015–0.03	0.03	0.03
	Levofloxacin	0.06	0.06	0.06
Moraxella catarrhalis (8)	Ulifloxacin	≤0.015–0.06	0.03	0.06
	Nalidixic acid	2–4	4	4
	Ciprofloxacin	0.12	0.12	0.12
	Moxifloxacin	0.12	0.12	0.12
	Trovafloxacin	0.03–0.06	0.03	0.06
	Grepafloxacin	0.06	0.06	0.06
	Levofloxacin	0.12	0.12	0.12

Cip^R: Ciprofloxacin resistant; Cip^S: Ciprofloxacin susceptible; MIC: Minimum inhibitory concentration; Nal^R: Nalidixic acid resistant.

Table 1. Antibacterial activity of ulifloxacin and other quinolones against Gram-negative bacterial strains [29] (cont.).

Organisms (no. of strains)	Antimicrobial agent	MIC (µg/ml)		
		Range	*50%*	*90%*
Legionella pneumophila (14)	Ulifloxacin	1	1	1
	Nalidixic acid	2	2	2
	Ciprofloxacin	0.25–0.5	0.25	0.5
	Moxifloxacin	1	1	1
	Trovafloxacin	0.12	0.12	0.12
	Grepafloxacin	0.5	0.5	0.5
	Levofloxacin	0.25	0.25	0.25
Campylobacter jejuni (10)	Ulifloxacin	0.12–>4	0.25	0.5
	Nalidixic acid	2–>32	4	8
	Ciprofloxacin	0.25–>4	0.5	1
	Moxifloxacin	0.12–>4	0.25	0.5
	Trovafloxacin	0.03–>4	0.06	0.12
	Grepafloxacin	0.12–>4	0.25	0.5
	Levofloxacin	0.12–>4	0.25	1

Cip^R: Ciprofloxacin resistant; Cip^S: Ciprofloxacin susceptible; MIC: Minimum inhibitory concentration; Nal^R: Nalidixic acid resistant.

The concentration of ulifloxacin in the CNS is undetectable after different protocols of prulifloxacin administration [36].

The pharmacokinetics of oral prulifloxacin after single- or multiple-dose administration have been evaluated in healthy Japanese and Caucasian volunteers. After administration of a single oral dose of prulifloxacin 600 mg, the maximum plasma concentrations (C_{max}) of ulifloxacin was 1.6 µg/ml within 1.0 h (T_{max}). The mean half-lives ranged from 10.6 to 12.1 h [37,38]. At steady state, the ulifloxacin C_{max} was 2.0 µg/ml after administration of prulifloxacin 600 mg once daily for 12 days, the corresponding T_{max} value was 0.75 h and half-life was 7.6 h [38]. At 48 h after a single dose of prulifloxacin 600 mg, ulifloxacin urinary concentrations were greater than 3 µg/ml [38]. Although the plasma levels of ulifloxacin are not higher than 2 µg/ml, the concentrations of ulifloxacin detected in some tissues and fluids are greater and longer lasting than those found in the circulating blood [19,34,35,38,39]; therefore, it is assumed that ulifloxacin reaches active concentrations in all the target compartments. At 48 h after administration, 17–23% of a single dose of prulifloxacin 300–600 mg was excreted as ulifloxacin in the urine and 17–29% in the feces [38]. Ulifloxacin clearance (~170 ml/min) is not dose dependent, and is higher than creatinine clearance, most likely due to the presence of an additional, active tubular secretion [38]. In patients with mild or moderate renal impairment, changes in ulifloxacin pharmacokinetic parameters after administration of prulifloxacin (prolonged T_{max}, increased area under the curve [AUC] and half-life decreased renal clearance) were correlated to the severity of renal impairment. Consequently, dosage adjustment in patients with any degree of renal impairment is suggested [36,40]. The *in vitro* binding of ulifloxacin (0.1–10 µg/ml) to proteins was 41–59%. Similar results were obtained in *in vivo* experiments [36].

Ulifloxacin has a good intracellular penetration. In an *in vitro* study with human polymorphonuclear leukocytes, the intracellular/extracellular concentration ratio achieved is 12.3, with an extracellular concentration of 20 µg/ml, slightly higher than ciprofloxacin [41]. In a mouse peritoneal macrophage model [42], the uptake of ulifloxacin was high, with cellular/extracellular ratios ranging from five to eight, depending on concentration and incubation time. These results are in agreement with the good killing activity on phagocytosed *S. aureus*, *K. pneumoniae* and *P. aeruginosa* [41,42].

Adverse reactions

Currently marketed fluoroquinolones present a favorable side-effect profile. The most common fluoroquinolone-related adverse events involve the gastrointestinal tract, CNS and skin reactions. These effects are generally mild and reversible on cessation of treatment [43]. Although phototoxicity is commonly associated with fluoroquinolones, only sparfloxacin has been reported to determine this reaction in nearly 8% of patients in clinical trials, and has been withdrawn from the market [44].

The widespread use of fluoroquinolones in the elderly, who are susceptible to cardiac arrhythmias due to underlying heart disease, metabolic derangement and use of antiarrhythmic agents that prolong the QT interval, has raised the issue of

Table 2. Antibacterial activity of ulifloxacin and other quinolones against Gram-positive bacterial strains [29].

Organisms (no. of strains)	Antimicrobial agent	MIC (μg/ml)		
		Range	*50%*	*90%*
Streptococcus pneumoniae (58)	Ulifloxacin	0.12–>4	2	4
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	0.5–4	1	2
	Moxifloxacin	0.03–0.5	0.12	0.25
	Trovafloxacin	≤0.015–0.5	0.12	0.25
	Grepafloxacin	0.06–0.5	0.25	0.5
	Levofloxacin	0.25–1	0.5	1
Streptococcus pyogenes (17)	Ulifloxacin	0.12–1	0.25	0.25
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	0.25–1	0.5	1
	Moxifloxacin	0.12–0.25	0.25	0.25
	Trovafloxacin	0.06–0.25	0.12	0.12
	Grepafloxacin	0.25–1	0.5	1
	Levofloxacin	0.5–1	1	1
Streptococcus agalactiae (16)	Ulifloxacin	0.25–1	0.25	1
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	0.5–2	1	1
	Moxifloxacin	0.12–0.25	0.12	0.25
	Trovafloxacin	0.12–0.25	0.12	0.25
	Grepafloxacin	0.25–0.5	0.5	0.5
	Levofloxacin	1–2	1	1
Staphylococcus aureus methicillin^{S} (10)	Ulifloxacin	0.25–2	0.5	0.5
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	0.5–2	0.5	0.5
	Moxifloxacin	0.06–0.12	0.06	0.06
	Trovafloxacin	≤0.015–0.06	0.03	0.03
	Grepafloxacin	0.06–0.25	0.06	0.12
	Levofloxacin	0.12–0.5	0.25	0.25
S. aureus methicillin^{R} (10)	Ulifloxacin	>4	>4	>4
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	>4	>4	>4
	Moxifloxacin	2–4	2	4
	Trovafloxacin	1–4	2	4
	Grepafloxacin	>4	>4	>4

Methicillin^{R}: Methicillin resistant; Methicillin^{S}: Methicillin susceptible; MIC: Minimum inhibitory concentration; Vancomycin^{R}: Vancomycin resistant; Vancomycin^{S}: Vancomycin susceptible.

Table 2. Antibacterial activity of ulifloxacin and other quinolones against Gram-positive bacterial strains [29] (cont.).

Organisms (no. of strains)	Antimicrobial agent	MIC (μg/ml)		
		Range	*50%*	*90%*
	Levofloxacin	>4	>4	>4
Enterococcus faecium vancomycin^S (11)	Ulifloxacin	1–4	2	2
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	1–4	2	2
	Moxifloxacin	0.25–2	1	1
	Trovafloxacin	0.25–1	1	1
	Grepafloxacin	0.5–>4	4	>4
	Levofloxacin	1–2	1	1
E. faecium vancomycin^R (7)	Ulifloxacin	4–>4	4	>4
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	4–>4	4	>4
	Moxifloxacin	2–>4	4	>4
	Trovafloxacin	2–>4	4	>4
	Grepafloxacin	4–>4	4	>4
	Levofloxacin	2–>4	4	>4
Enterococcus faecalis vancomycin^S (11)	Ulifloxacin	0.5–4	2	4
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	0.5–4	1	1
	Moxifloxacin	0.12–1	0.25	0.25
	Trovafloxacin	0.12–2	0.25	0.5
	Grepafloxacin	0.25–>4	0.5	0.5
	Levofloxacin	0.5–2	1	2
E. faecalis vancomycin^R (10)	Ulifloxacin	>4	>4	>4
	Nalidixic acid	>32	>32	>32
	Ciprofloxacin	>4	>4	>4
	Moxifloxacin	>4	>4	>4
	Trovafloxacin	4–>4	>4	>4
	Grepafloxacin	>4	>4	>4
	Levofloxacin	>4	>4	>4

Methicillin^R: Methicillin resistant; Methicillin^S: Methicillin susceptible; MIC: Minimum inhibitory concentration; Vancomycin^R: Vancomycin resistant; Vancomycin^S: Vancomycin susceptible.

cardiac safety of the newer fluoroquinolones. This issue has been further stressed by the unexpected removal from the market of grepafloxacin for cardiotoxic effect [45].

After prulifloxacin treatment, the more frequently reported adverse reactions were gastric pain, diarrhea, nausea and cutaneous rash [19]. They were generally of mild or moderate severity. The phototoxic potential of prulifloxacin was assessed in a specific crossover clinical trial performed in healthy volunteers and was shown to be comparable with that of ciprofloxacin [36].

The risk of cardiac toxicity, and in particular the potential to prolong the QTc interval, was assessed for ulifloxacin both *in vitro*, on the human ether-a-go-go-related gene (hERG)

potassium channel in comparison with ciprofloxacin and moxifloxacin, and *in vivo* in the conscious dog monitored by telemetry. The very small reduction in hERG current amplitude, lower than the reference compounds, together with the absence of prolonged QTc interval *in vivo* following 5 days of repeated oral treatment (150 mg/kg once daily), suggest that prulifloxacin has no significant effects on the QT interval [46,47].

Drug interactions

The concomitant oral administration of antiacids, cimetidine, and iron-containing supplements reduces the absorption of prulifloxacin [48]. Some quinolones may affect theophylline bioavailability. Ciprofloxacin can increase theophylline serum concentrations up to 300% [49,50]. Although prulifloxacin shows a weak interaction with theophylline, monitoring of theophylline plasma levels is recommended during coadministration of the two drugs.

Clinical efficacy

The results of preclinical and tissue penetration studies suggested to evaluate the efficacy and safety of prulifloxacin 600 mg once-daily doses in several comparative trials carried out in patients with acute uncomplicated and complicated UTI and acute exacerbations of chronic bronchitis (AECB).

Uncomplicated urinary tract infection (simple cystitis)

A published study was carried out in 239 women with acute uncomplicated cystitis treated with prulifloxacin 600 mg in comparison with pefloxacin 800 mg single doses [51]. Eligible female patients were nonpregnant, at least 18 years of age, with clinical signs and symptoms of acute UTI (any combination of dysuria, urgency, frequency or suprapubic pain).

The main exclusion factors were recurrent cystitis, pyelonephritis, complicated UTI, administration of drugs such as theophylline or fenbufen in the 2 weeks prior to enrollment. Patients were evaluated at baseline and re-evaluated at 5–7 days after completion of therapy and after 4 weeks. Microbiological eradication and clinical cure or improvement were the primary and secondary end points assessed.

At baseline, the onset of a patient's symptoms was not more than 48–72 h prior to study entry. After the end of therapy, the microbiological eradication was similar in patients receiving prulifloxacin or pefloxacin (97.4 vs 92.2%). Similarly, high eradication rates were obtained for the two drugs after 1 month post therapy (97.4 vs 96.5%). The clinical efficacy rates were also similar, with only 7.8 and 15.7% failures in the prulifloxacin- and pefloxacin-treated groups, and 2.6 and 3.5% 4 weeks after dosing. A study comparing a single dose of prulifloxacin 600 mg and ciprofloxacin 500 mg in 251 patients with uncomplicated UTI was also carried out [52].

At the first assessment, 5–7 days after treatment, the microbiological eradication was achieved in 97.2% of patients treated with prulifloxacin and ciprofloxacin. At the follow-up visit, 1 month after the end of therapy, the eradication rate was reported in 95.2 and 95.4% of prulifloxacin- and ciprofloxacin-treated patients. High rates of clinical success were always observed with both drugs.

Complicated urinary tract infections

Two trials were performed in order to compare the efficacy of a once-daily prulifloxacin 600 mg 10-day course versus ciprofloxacin 500 mg twice daily [53], or amoxicillin plus clavulanic acid 1 g twice daily [54] in patients with complicated lower UTI. In both studies, patients were assessed 5–7 days and 4 weeks after treatment. The primary and secondary end points were bacteriological eradication and clinical success, respectively.

In the published, double-blind, double-dummy study comparing prulifloxacin versus ciprofloxacin and enrolling 257 patients, the rate of microbiological eradication in the intent-to-treat population, assessed 5–7 days after treatment, was 90.8 versus 77.8% [53]. This difference was statistically significant ($p = 0.008$). At the follow-up, the microbiological success rates were 75.3 versus 72.2% for prulifloxacin and ciprofloxacin, respectively. At the first assessment, the clinical success rate was 94.8% for prulifloxacin versus 93.3% for ciprofloxacin.

Bacteriological and clinical results of the randomized open study comparing prulifloxacin with amoxicillin/clavulanic acid in 225 patients were similar in both treatment groups [54]. Microbiological eradication was 93.1 and 95.1% at the first visit and 93.5 and 93.7 at the follow-up, respectively.

Acute exacerbations of chronic bronchitis

The *in vitro* activity of ulifloxacin against a wide range of microorganisms associated with community-acquired respiratory tract infections suggested prulifloxacin as a promising therapeutic option in the treatment of patients with AECB. Two studies have been carried out according to the criteria recommended in the guidelines for the evaluation of new anti-infective drugs for the treatment of respiratory tract infections [55–57].

The comparative efficacy of prulifloxacin 600 mg once daily and ciprofloxacin 500 mg twice daily, both administered for 10 days, was evaluated in a multicenter, double-blind, double-dummy study [55]. In total, 235 patients took part in the trial (117 prulifloxacin and 118 ciprofloxacin). Efficacy was assessed by comparing the clinical response at the post-treatment visit versus the baseline assessment for cough, dyspnea, sputum volume and appearance. The microbiological response was also assessed in sputum specimens. Clinical success was observed in 84.7 and 85% of the patients in the prulifloxacin and ciprofloxacin groups, respectively. The eradication potency showed by the two drugs was alike for the most frequently isolated strains, including *H. influenzae*, *S. pneumoniae*, *K. pneumoniae* and *P. aeruginosa*.

Although the *in vitro* studies showed a high activity against Gram-negative strains, data emerging from this clinical trial in patients treated with prulifloxacin evidenced an interesting

eradication rate of *S. pneumoniae* (eight out of nine, 88.9% eradication) in comparison with the reference medication (nine out of 12, 75% eradication). However, the small sample of strains detected during the trial does not allow any definite conclusions to be drawn [55].

Both treatment regimens were well tolerated, since only mild or moderate adverse drug reactions were observed. According to the authors' opinion, the results of the trial demonstrated that a 10-day course of prulifloxacin is as effective and safe as ciprofloxacin in patients with AECB.

In the other multicenter, double-blind, double-dummy study, 214 patients with AECB were enrolled [56]. They were treated for 10 days with prulifloxacin 600 mg once daily in comparison with twice-daily amoxicillin/clavulanic acid 1 g. The therapeutic results were similar in the two groups, with the clinical success rates at the end of the treatment of 92.5 and 93.4% for prulifloxacin and amoxicillin/clavulanic acid, respectively. The end-of-treatment microbiological success rates were also similar in the two groups [56].

Expert commentary & five-year view

Although several studies have established the efficacy of fluoroquinolones against a range of bacterial pathogens, there is continued interest in the development of new fluoroquinolones in order to improve antibacterial activity and overcome bacterial resistance.

Ulifloxacin is the active compound of prulifloxacin, the lipophilic prodrug. *In vitro* studies have shown that ulifloxacin is highly active against Gram-negative bacteria including *Enterobacteriaceae*, *P. aeruginosa*, *H. influenzae* and *M. catarrhalis*. In addition, a recent *in vitro* study indicated that prulifloxacin represents the most powerful anti-pseudomonal drug available today [57]. The drug is also active against Gram-positive bacteria such as methicillin-susceptible *S. aureus*, *S. pyogenes* and *S. pneumoniae*.

Ulifloxacin has an extended elimination half-life allowing for once-daily dosing, and it penetrates extensively into the respiratory tissues. Lung tissue concentrations exceed those than in plasma or serum, and the drug persists in the lung tissue for 24 h after a single dose [19]. Although the *in vitro* activity of ulifloxacin against *S. pneumoniae* is lower than the activity demonstrated by the newer fluoroquinolones, the penetration and persistence of prulifloxacin into the pulmonary tissues lead to high drug levels responsible for the eradication of most of *S. pneumoniae* strains present in the sputum of patients with AECB.

The high urinary concentrations of ulifloxacin (>3 µg/ml at 48 h after a single dose of prulifloxacin 600 mg) suggest its use in UTIs.

Clinical evidence clearly indicated that prulifloxacin 600 mg shows clinical and bacteriological efficacy, with high eradication and clinical success rates, at least as high as those of the comparators, ciprofloxacin, co-amoxiclav and pefloxacin, in the treatment of patients with UTI and AECB.

Following treatment with prulifloxacin 600 mg, the incidence of adverse reactions was shown to be equivalent to the best reference medication widely employed in respiratory and UTIs. Adverse effects were generally mild, with gastric pain, diarrhea, nausea and cutaneous rash being the most frequent.

Prulifloxacin has been approved for the treatment of acute uncomplicated and complicated UTI, and AECB. A single administration in uncomplicated UTI and an up to 10-day once-daily regimen in complicated UTI and AECB are suggested. The drug is available in 600 mg tablets for oral use.

Fluoroquinolones are an important class of drugs for the treatment of gastrointestinal, respiratory infections and UTIs. Probably, the increase of antibiotic resistance will be retained, thus in the next few years these drugs should maintain their important role in the treatment of such infections.

Conversely, the future development of new fluoroquinolones is not predictable, and the toxicity could be the most important barrier. Therefore, the current nontoxic fluoroquinolones will keep their remarkable therapeutic role, and the use of prulifloxacin, according to its antimicrobial spectrum, could be further investigated in other diseases concerning respiratory, urinary and gastrointestinal tract infections.

Key issues

- Prulifloxacin (UNIDROX®, Angelini) is a new thiazetho-fluoroquinolone.
- Prulifloxacin has a broad antimicrobial spectrum shown to be more active than other fluoroquinolones against Gram-negative bacteria.
- Prulifloxacin has a long serum half-life and thus, can be orally administered at 24-h intervals.
- Prulifloxacin concentrations in lung and urine are two- to five-times higher than in serum.
- Clinical studies have demonstrated very good efficacy in the treatment of acute uncomplicated and complicated urinary tract infections and acute exacerbations of chronic bronchitis.
- Prulifloxacin is well tolerated, with gastric pain, diarrhea, nausea and cutaneous rash as the most frequent adverse reactions in patients receiving the drug in single-shot treatment or in a 10-day regimen.

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