Eur J Clin Microbiol Infect Dis (1998) 17:405–412

Review

Bacteriological Activity of Trovafloxacin, a New Quinolone, against Respiratory Tract Pathogens

J.-C. Pechère, T. D. Gootz

Abstract The use of established fluoroquinolones, such as ciprofloxacin and ofloxacin, as empirical therapy for the treatment of moderate-to-severe respiratory tract infections is limited by their poor activity against gram-positive and atypical pathogens. Data from in vitro susceptibility studies and in vivo animal protection models suggest that the new fluoroquinolone, trovafloxacin, compared with ciprofloxacin and ofloxacin offers equivalent activity against gram-negative pathogens and improved activity against gram-positive pathogens. In particular, susceptibility data indicate that trovafloxacin is at least 16-fold more potent than either ciprofloxacin or ofloxacin against penicillin-susceptible and penicillin-resistant strains of *Streptococcus pneumoniae*. Other susceptible pathogens include *Streptococcus pyogenes*, vancomycin-susceptible *Enterococcus faecalis* and the atypical respiratory pathogens *Legionella pneumophila, Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. In vivo studies involving models of protection against acute systemic infection and pneumococcal pneumonia in mice, and Legionnaires' disease in guinea pigs, indicate that the antibacterial spectrum observed for trovafloxacin in vitro extends to the in vivo setting. Together, these findings suggest that trovafloxacin may offer clinical efficacy against respiratory pathogens superior to that of ciprofloxacin and of ofloxacin, and may find a useful role as empiric therapy in both the community and hospital setting.

Introduction

High incidences of penicillin resistance [1], escalating β-lactamase production and poor activity against atypical pathogens are increasingly limiting the use of β-lactam antibiotics for the empiric treatment of respiratory tract infections. Macrolides have been used as alternative agents, but there is growing concern about the emergence of resistance to this class of antibiotics, particularly with *Streptococcus pneumoniae*. Clinicians are now searching for other antibiotics that can provide cost-effective, ideally single-agent, empiric therapy for moderate-to-severe community- and hospital-acquired respiratory infections.

J.-C. Pechère (✉)
Department of Genetics and Microbiology,
University of Geneva Medical School, Avenue de Champel 9,
CH-1211 Geneva 4, Switzerland

T. D. Gootz
Central Research Division, Pfizer Inc, Eastern Point Road,
Groton, CT 06340, USA

The established fluoroquinolone antibiotics exhibit excellent activity against a broad spectrum of gram-negative pathogens, resulting in their use as monotherapy for acute exacerbations of chronic bronchitis and as part of a combination therapy for hospital-acquired pneumonia. By contrast, the activity of established fluoroquinolones is only moderate against *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*; thus their use as first-line therapy for community-acquired pneumonia is not widely accepted.

There is a need, therefore, for new fluoroquinolones that offer improved activity against gram-positive and atypical respiratory pathogens. Trovafloxacin is a novel fluoronaphthyridone with a similar structure to existing fluoroquinolones. This article reviews the preclinical evaluation of trovafloxacin against respiratory pathogens that are isolated from widely diverse geographical locations.

Chemical Structure

Most currently available quinolone antibacterial agents possess the same core structure (Figure 1a). Experience gained during the development of the quinolones has confirmed the importance of the nitrogen at N-1, the ketone at C-4, the carboxylic group at C-3 and the fluoride at C-6 for potent antimicrobial activity. Most of the variation in structure and activity within this family of compounds is derived from substitutions at positions N-1 and C-7 [2]. Trovafloxacin (CP-99,219), a fluoronaphthyridone, while retaining the quinolone core structure, has a combination of structural moieties not found in other fluoroquinolones: a 3-azabicyclo[3.1.0]hexyl substitution at C-7 and a 2,4-difluorophenyl group at the N-1 position (Figure 1b). The nitrogen atom at the C-8 position, which renders trovafloxacin a naphthyridone, appears to be associated with a long elimination half-life [3].

Mode of Action of Trovafloxacin

Trovafloxacin, in common with the established fluoroquinolones, elicits its bactericidal action by interacting with and inhibiting the action of bacterial DNA gyrase, i.e., topoisomerase II [4, 5]. A second topoisomerase, topoisomerase IV, appears to be a secondary target for fluoroquinolones in *Escherichia coli* [6] and *Neisseria gonorrhoeae* [7], and the primary target for ciprofloxacin and trovafloxacin in *Staphylococcus aureus* [8], and *Streptococcus pneumoniae* [9]. The agent does not inhibit eukaryotic topoisomerase II and, therefore, is not cytotoxic towards human cells [10].

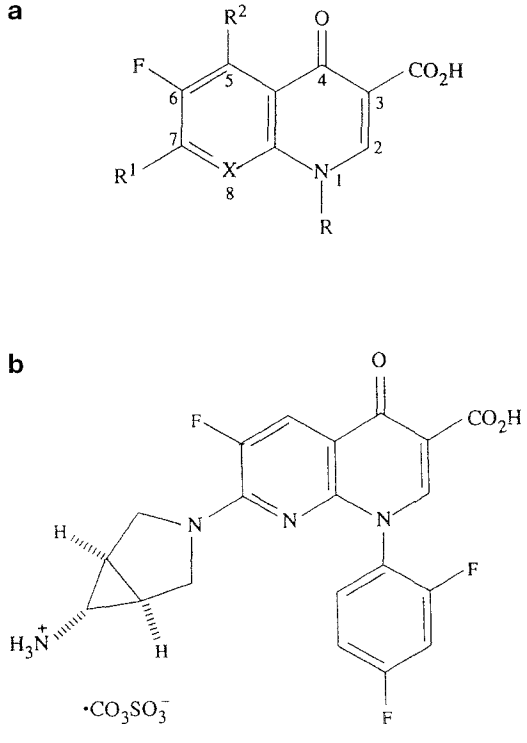

Figure 1 Chemical structures of (**a**) quinolone antibiotics and (**b**) trovafloxacin

Mechanisms of Resistance to Fluoroquinolones

The dominant factor in the emergence of resistance to fluoroquinolones appears to be mutation of DNA gyrase in gram-negative and of topoisomerase IV in gram-positive organisms [3]. An additional mechanism of resistance includes the presence of efflux transporters [11–13], which actively export fluoroquinolones from within the bacteria. The role of porins and outer membrane permeability is more questionable.

Studies in *Streptococcus pneumoniae* [9], *Staphylococcus aureus* [14] and *Pseudomonas aeruginosa* [15] have indicated that trovafloxacin has a reduced potential to select fluoroquinolone resistance compared with other agents, such as ciprofloxacin.

Antimicrobial Activity in Vitro

A large number of microbiological studies have evaluated the in vitro susceptibilities of gram-negative, gram-positive and atypical respiratory pathogens to trovafloxacin, ciprofloxacin and ofloxacin. Typically, these studies determined, using National Committee for Clinical Laboratory Standards recommended procedures [16], the minimal concentrations of one or more of the antibiotics that inhibit the growth of 90% of the bacterial isolates studied (MIC_{90}), enabling median MIC_{90} values to be calculated.

Gram-Positive Respiratory Pathogens. The in vitro data indicate that trovafloxacin offers inhibitory activity that is markedly superior to that of either ciprofloxacin or ofloxacin against most gram-positive pathogens (Table 1). For both penicillin-susceptible and -resistant (MIC ≥ 0.5 mg/l) *Streptococcus pneumoniae* strains the median MIC_{90} is 0.12 mg/l, with a maximum recorded MIC of 0.5 mg/l and is at least 16-fold more potent than either ciprofloxacin or ofloxacin. Maximum MICs of 8 mg/l were recorded for both ciprofloxacin and ofloxacin. Methicillin-susceptible *Staphylococcus aureus* is highly susceptible to trovafloxacin (median MIC_{90} 0.06 mg/l) compared with ciprofloxacin (0.75 mg/l) and ofloxacin (0.5 mg/l). Likewise, trovafloxacin is at least 12- and eightfold more potent than ciprofloxacin and ofloxacin, respectively, against methicillin-resistant *Staphylococcus aureus*, and at least eightfold more potent against ciprofloxacin-resistant isolates; the clinical significance of these differences remains to be determined. Superior activity of trovafloxacin against *Streptococcus pyogenes* has also been detected. Some isolates of enterococci are susceptible in vitro to trovafloxacin. However, this activity is much less in vancomycin-resistant strains [18] and tro-

Table 1 Comparative in vitro activities of trovafloxacin, ciprofloxacin and ofloxacin against gram-positive respiratory pathogens

Organism	No. of isolates	MIC_{90} (mg/l)		References
		Range	Median	
Streptococcus pneumoniae, pen-S				
Trovafloxacin	1867	0.06–0.25	0.12	10, 17–33, (S. Kocagoz et al., 35th ICAAC, 1995, Abstract no. F231)
Ciprofloxacin	1847	1.0–8.0	2.0	9, 17–22, 24–33, (S. Kocagoz et al., 35th ICAAC, 1995, Abstract no. F231)
Ofloxacin	1427	2.0–4.0	4.0	9, 17, 19, 20, 27–29, 33, (S. Kocagoz et al., 35th ICAAC, 1995, Abstract no. F231)
Streptococcus pneumoniae, pen-R				
Trovafloxacin	498	0.12–0.25	0.12	8, 17, 21, 28, 33
Ciprofloxacin	498	1.0–8.0	2.0	9, 17, 21, 28, 33
Ofloxacin	343	2.0–4.0	4.0	17, 28, 33
Streptococcus pyogenes				
Trovafloxacin	242	0.06–0.5	0.12	9, 18, 20, 24, 25, 30–32, 34, 37
Ciprofloxacin	242	0.5–4.0	0.75	9, 18, 20, 24, 25, 30–32, 34, 37
Ofloxacin	35	1.0–2.0	1.5	20, 34
Staphylococcus aureus, MSSA				
Trovafloxacin	666	≤0.015–0.5	0.06	9, 18–20, 22–26, 30, 31, 34–37
Ciprofloxacin	646	0.5–8.0	0.75	9, 18–20, 22–26, 30, 31, 34–37
Ofloxacin	194	0.25–0.5	0.5	19, 20, 31, 34, 35
Staphylococcus aureus, MRSA, CRSA				
Trovafloxacin	487	1.0–8.0	2.0	18–20, 22–26, 30, 32, 34–38
Ciprofloxacin	452	>4–>128	>16	18–20, 22–26, 30, 32, 34–38
Ofloxacin	134	2–>16	16	19, 20, 31, 34, 36
Enterococcus faecalis, van-S				
Trovafloxacin	574	0.25–8	2.0	9, 18–20, 23–26, 30–32, 34, 35, 37, 39
Ciprofloxacin	537	1.0–32	2.0	9, 18–20, 23–26, 30–32, 34, 35, 37, 39
Ofloxacin	188	2.0–8.0	4.0	19, 20, 31, 34, 36
Enterococcus faecalis, van-R				
Trovafloxacin	33	8–16	8	23, 40, 41, Pfizer data on file
Ciprofloxacin	19	>4–32	16	40, 41
Ofloxacin	12	>8	> 8	40

CRSA, ciprofloxacin-resistant *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; pen-R, penicillin-resistant (MIC ≥0.5 mg/l); pen-S, penicillin-susceptible (MIC <0.5 mg/l); van-S, vancomycin-susceptible

vafloxacin, in common with other recently developed fluoroquinolones such as sparfloxacin, was unable to reduce intracellular viability of vancomycin-resistant *Enterococcus faecium* [39, 40].

Gram-Negative Respiratory Pathogens. Overall, trovafloxacin is as active in vitro as ciprofloxacin and more so than ofloxacin against these pathogens (Table 2). Against *Haemophilus influenzae*, *Moraxella catarrhalis* and *Escherichia coli*, for example, the median MIC_{90} values for trovafloxacin (0.015, 0.03 and 0.06 mg/l, respectively) are comparable to those of ciprofloxacin and are half those of ofloxacin. The maximum MICs recorded for trovafloxacin were 0.12, 0.06 and 33 mg/l. Against *Pseudomonas aeruginosa*, trovafloxacin and ciprofloxacin (median MIC_{90} 2 mg/l) are both fourfold more potent than ofloxacin. The potency of trovafloxacin exceeds that of ciprofloxacin in the case of *Stenotrophomonas maltophila.*

Against most of the other gram-negative respiratory pathogens tested, trovafloxacin offers an activity generally between that of ciprofloxacin and ofloxacin. Overall, the data indicate that the activity of trovafloxacin is comparable to the activities of ciprofloxacin and ofloxacin across a broad spectrum of gram-negative pathogens.

Atypical Respiratory Pathogens. The median MIC_{90}s derived from in vitro susceptibility studies indicate that trovafloxacin is as active as ofloxacin against *Chlamydia pneumoniae* and is more active against *Legionella pneumophila* and *Mycoplasma pneumoniae* (Table 3). In vitro studies also show that trovafloxacin is more active than ciprofloxacin against *Legionella pneumophila* and *Mycoplasma pneumoniae.*

Animal Models of Infection

In an acute systemic infection model, mice were infected with one of a range of gram-positive and gram-negative organisms administered via intraperitoneal injection [45]. Each treatment group of ten mice

Table 2 Comparative in vitro activities of trovafloxacin, ciprofloxacin, and ofloxacin against gram-negative respiratory pathogens

Organism	No. of isolates	MIC_{90} (mg/l)		References
		Range	Median	
Haemophilus influenzae				
Trovafloxacin	403	≤0.004–0.05	0.015	9, 18–20, 22, 26, 30–32
Ciprofloxacin	403	≤0.004–0.05	0.015	9, 18–20, 22, 26, 30–32
Ofloxacin	67	0.016–0.03	0.023	19, 34
Moraxella catarrhalis				
Trovafloxacin	304	0.008–0.06	0.03	9, 18, 19, 22, 25, 26, 30, 31, 34
Ciprofloxacin	304	0.03–1.0	0.06	16, 18, 19, 22, 25, 26, 30, 31, 34
Ofloxacin	53	0.03–0.12	0.075	19, 34
Pseudomonas aeruginosa				
Trovafloxacin	566	1.0–>16	2.0	9, 19, 20, 24, 25, 30–32, 34, 37, 41
Ciprofloxacin	566	0.5–>16	2.0	9, 19, 20, 24, 25, 30–32, 34, 37, 41
Ofloxacin	357	4.0–>16	>8	19, 20, 31, 34, 35, 41
Escherichia coli				
Trovafloxacin	476	<0.015–4.0	0.06	9, 19, 20, 22, 25, 26, 30–32, 3, 37
Ciprofloxacin	476	<0.015–0.5	0.06	9, 19, 20, 22, 25, 26, 30–32, 3, 37
Ofloxacin	193	0.05–0.12	0.12	19, 20, 31, 35, 37
Klebsiella pneumoniae				
Trovafloxacin	331	0.06–1.0	0.12	16, 20, 22, 26, 30–32, 35
Ciprofloxacin	331	0.06–4.0	0.06	16, 20, 22, 26, 30–32, 35
Ofloxacin	95	0.12–2.0	1.0	20, 31, 35
Enterobacter cloacae				
Trovafloxacin	242	0.05–2.0	1.6	16, 20, 22, 30–32, 34, 35
Ciprofloxacin	242	0.01–4.0	0.31	16, 20, 22, 30–32, 34, 35
Ofloxacin	90	0.06–4.0	2.12	20, 31, 34, 35
Morganella morganii				
Trovafloxacin	195	0.12–2.0	0.5	16, 20, 22, 25, 26, 30–32, 34, 35
Ciprofloxacin	195	≤0.015–1.0	0.12	16, 20, 22, 25, 26, 30–32, 34, 35
Ofloxacin	46	0.12–2.0	0.19	20, 31, 34, 35
Proteus mirabilis				
Trovafloxacin	298	0.12–4.0	0.5	16, 20, 22, 25, 26, 30–32, 34, 35
Ciprofloxacin	298	0.03–1.0	0.06	16, 20, 22, 25, 26, 30–32, 34, 35
Ofloxacin	80	0.06–0.25	0.12	20, 31, 34, 35
Serratia marcescens				
Trovafloxacin	211	0.25–16	2.5	16, 20, 26, 30–32, 34, 35
Ciprofloxacin	211	0.12–>8	1.0	16, 20, 26, 30–32, 34, 35
Ofloxacin	100	0.5–>8	2.3	20, 31, 34, 35
Stenotrophomonas maltophilia				
Trovafloxacin	227	0.5–>8	2.0	20, 25, 30, 31, 35, 41, 42
Ciprofloxacin	227	1.0–16	>8	20, 25, 30, 31, 35, 41, 42
Ofloxacin	197	>8–>16	>8	20, 25, 30, 31, 35, 42

Table 3 Comparative in vitro activities of trovafloxacin, ciprofloxacin, and ofloxacin against atypical respiratory pathogens

Organism	No. of isolates	MIC_{90} (mg/l)		References
		Range	Median	
Chlamydia pneumoniae				
Trovafloxacin	13	1.0	1.0	43
Ofloxacin	13	1.0	1.0	43
Legionella pneumophila				
Trovafloxacin	155	≤0.004–0.06	0.008	19, 31, 44
Ciprofloxacin	133	0.015–0.06	0.038	19, 31
Ofloxacin	155	0.015–0.06	0.032	19, 31, 44
Mycoplasma pneumoniae				
Trovafloxacin	50	0.12–0.25	0.185	19, 45
Ciprofloxacin	10	1.0	1.0	19
Ofloxacin	50	1.0	1.0	19, 45

Table 4 In vivo activity of orally-delivered trovafloxacin against gram-positive pathogens in mice [46]

Challenge (strain)	PD_{50} (95% confidence limits, mg/kg)		
	Trovafloxacin	Ciprofloxacin	Ofloxacin
Streptococcus pneumoniae (02J0025)	1.3 (0.6–2.6)	>50	>50
Streptococcus pneumoniae (Pocidalo 4241)	9.7 (5.8–16.1)	>50	>50
Staphylococcus aureus (01A0400), MSSA	2.9 (3.7–11.0)	13.1 (8.2–21.1)	NA
Staphylococcus aureus (01A0129)	2.0 (1.1–3.6)	1.1 (1.0–3.4)	NA
Staphylococcus aureus (01A1080)	42.6 (40.8–69.1)	>50	>50
Staphylococcus aureus (01A1063)	>50	>50	>50
Streptococcus pyogenes (ATCC12384)	3.0 (1.7–5.4)	8.7 (4.8–15.5)	>50
Enterococcus faecalis (03A0131)	6.4 (3.7–11.0)	>50	>50

NA, not available

received an oral dose of antibiotic administered 0.5 and 4 h after infection. The numbers of mice that survived until day 4 were determined and used to calculate the protective dose for 50% of the animals (PD_{50}).

Gram-Positive Respiratory Pathogens. Trovafloxacin provided effective treatment in the acute systemic infection model [44] and was generally superior to ciprofloxacin or ofloxacin (Table 4). The PD_{50} values indicate that trovafloxacin was particularly effective against two strains of *Streptococcus pneumoniae*, whereas both ciprofloxacin and ofloxacin proved ineffective even at the highest dose employed (50 mg/kg/day).

Against a methicillin-resistant *Staphylococcus aureus* strain (01A0129), trovafloxacin and ciprofloxacin appeared to be equally effective. However, data for other *Staphylococcus aureus* strains highlight clear differences in potency among the fluoroquinolones. Trovafloxacin was more than fourfold more effective than ciprofloxacin against a methicillin-susceptible strain (01A0400) and was the only fluoroquinolone to demonstrate activity against one of the fluoroquinolone-resistant (trovafloxacin MIC = 3.12 mg/l) strains (01A1080). None of the fluoroquinolones exhibited in vivo activity against strain 01A1063, which is highly resistant to fluoroquinolones (trovafloxacin MIC = 25 mg/l).

The pattern of superior activity for trovafloxacin extends to the other pathogens investigated. Trovafloxacin was nearly threefold more active than ciprofloxacin in protecting mice against *Streptococcus pyogenes* infection and was effective against *Enterococcus faecalis*, against which both ciprofloxacin and ofloxacin proved ineffective at the highest dose tested. In these tests, the efficacy observed with trovafloxacin generally paralleled its in vitro potency against the infecting pathogen.

Two additional animal protection studies have demonstrated the relative activities of trovafloxacin, ciprofloxacin and ofloxacin in treating infections caused by *Streptococcus pneumoniae*. In one study, two groups of ten mice were infected intranasally with *Streptococcus pneumoniae* strain Pocidalo 4241 [47]. Oral twice-daily therapy with trovafloxacin or ciprofloxacin was initiated 18 h after infection and maintained for 3 days. Survivors were monitored over 10 days, after which the PD_{50} was calculated. The results suggest that trovafloxacin is more potent in vivo than ciprofloxacin. Trovafloxacin protected 90–100% of the animals with oral therapies of 12.5–50 mg/kg, giving a PD_{50} of 2.1 mg/kg. In contrast, ciprofloxacin protected only 20–30% of challenged animals at doses of 75–100 mg/kg.

A second study employed a similar mouse pneumonia model to compare the activities of trovafloxacin, ciprofloxacin and ofloxacin against one penicillin-susceptible *Streptococcus pneumoniae* strain (Pocidalo 4241) in immunocompetent mice and three penicillin-resistant isolates in leucopenic mice [48]. Therapy began 6 h and 3 h, respectively, after infection and involved the administration of two subcutaneous doses per day for 3 days. Untreated, control mice died by day 3 post-challenge in this model. Survival rates with trovafloxacin were significantly greater than with ciprofloxacin or ofloxacin. A once-daily 25 mg/kg dose of trovafloxacin protected 91% of the mice infected with the penicillin-susceptible strain 4241 and 66–100% of mice infected with penicillin-resistant strains. By comparison, in the case of ciprofloxacin, the next most effective agent, a dose of 100 mg/kg protected only 23% and 58% of mice, respectively.

An indication of the greater clinical potential of trovafloxacin against *Streptococcus pneumoniae* is also provided by its superior distribution into the lung tissues compared with ciprofloxacin. Girard et al. [46] found that, in mice infected with strain 4241, the maximum concentration of trovafloxacin in lung tissue was at least twice that of ciprofloxacin, and that the half-life of trovafloxacin was over threefold greater. Consequently, the area under the lung concentration–time curve for trovafloxacin was nearly sixfold greater than for ciprofloxacin.

Table 5 In vivo activity of orally-delivered trovafloxacin against gram-negative pathogens in mice [46]

Challenge (strain)	PD_{50} (95% confidence limits, mg/kg)		
	Trovafloxacin	Ciprofloxacin	Ofloxacin
Enterobacter cloacae (67B0153)	12.5 (6.7–23.1)	18.1 (7.6–42.8)	NA
Escherichia coli (51A0266)	2.3 (0.8–6.1)	<0.8	<0.8
Klebsiella pneumoniae (ATCC 43816)	1.1 (0.4–1.8)	2.5 (1.8–3.3)	NA
Morganella morganii (97A0096)	16.8 (7.6–37.3)	4.6 (2.3–9.2)	NA
Pseudomonas aeruginosa (52A0266)	6.5 (3.5–12.0)	1.2 (0.5–2.6)	1.9 (0.8–4.7)
Proteus mirabilis (57C0175)	5.6 (3.0–10.3)	6.9 (3.8–12.9)	17.5 (7.7–39.8)

NA, not available

Gram-Negative Respiratory Pathogens. The acute systemic infection model that established superior potency of trovafloxacin against gram-positive respiratory pathogens has also shown that trovafloxacin, ciprofloxacin and ofloxacin offer broadly comparable in vivo activities against important gram-negative respiratory pathogens [46]. Trovafloxacin was slightly more active against *Enterobacter cloacae* and *Klebsiella pneumoniae* than ciprofloxacin, but slightly less so than ciprofloxacin and ofloxacin against *Escherichia coli* and *Pseudomonas aeruginosa*, and markedly less effective than ciprofloxacin against *Morganella morganii* (Table 5). The activity of trovafloxacin against *Proteus mirabilis* was slightly higher than that of ciprofloxacin and markedly higher than that of ofloxacin.

Atypical Respiratory Pathogens. The in vivo activity of trovafloxacin against *Legionella pneumophila* has been explored and compared with that of ofloxacin in an animal model featuring lethal lung infections with this atypical pathogen [44]. Guinea pigs infected intratracheally with *Legionella pneumophila* serogroup 1 strain F889 received a single dose of trovafloxacin (7.5 mg/kg), ofloxacin (10 mg/kg) or saline, administered intraperitoneally once daily for 5 days.

All guinea pigs treated with trovafloxacin or ofloxacin survived 14 days after infection, whereas none of the control guinea pigs survived more than 5 days. No significant differences in lung histology were noted between the trovafloxacin- and ofloxacin-treated animals who survived. Only two of the seven lung samples from the trovafloxacin treatment group were positive for *Legionella pneumophila*, compared with three of the seven lung samples from the ofloxacin group. The major difference observed between the treatment groups was slower weight gain in the trovafloxacin group, which could have been attributable to lower initial weights in this group before infection [44].

A similar study involving the same experimental model has shown that trovafloxacin (5 mg/kg/day) completely eradicated *Legionella pneumophila* from the lungs and spleen in all animals after 4–5 days of treatment and that *Legionella* could not be recovered after 28 days (E. Millas et al., 36th ICAAC, 1996, Abstract no. E76).

The in vitro susceptibility data, combined with better in vivo activity than either ciprofloxacin or ofloxacin, led Edelstein et al. [44] to conclude that trovafloxacin is one of the most active antimicrobial agents tested against *Legionella* species, being more effective than ciprofloxacin and other antibiotics such as azithromycin, erythomycin, clavulanic acid and tazobactam.

Tissue and Intracellular Penetration of Trovafloxacin

Positron emission tomography performed in healthy volunteers revealed that the peak concentration of trovafloxacin in lung following a 200 mg dose was 22.5±7.1 μg/g [A.J. Fischman et al. 37th ICAAC, 1997, Abstract no. A68]. Edelstein et al. [44] showed that the maximum concentration of trovafloxacin in guinea pig alveolar macrophages in vitro was 28-fold greater than the concentration in extracellular fluid. Concentration in serum, alveolar macrophages, epithelial lining and bronchial mucosa of 1.01 mg/kg, 0.37, 10.23 and 0.93 mg/l, respectively, have been recorded 24 h after a single oral dose of 200 mg trovafloxacin in humans [47]. These concentrations exceeded even the highest median MIC_{90} values of respiratory pathogens presented in Tables 1–3, and should be sufficiently high to ensure bacterial eradication.

Conclusions

Fluoroquinolones comprise just one of many classes of antimicrobial agents used to treat the gamut of community- and hospital-acquired respiratory tract infections in humans. Although ciprofloxacin and ofloxacin find some use in the treatment of acute exacerbations of chronic bronchitis and in combination with other agents, for hospital-acquired pneumonia, their more widespread use for community-acquired pneumonia is limited by their relatively poor activity against pneumococci and atypical pathogens. Further, the use of pres-

ently marketed fluoroquinolones has been accompanied by the emergence of fluoroquinolone-resistant *Staphylococcus aureus* and *Streptococcus pneumoniae* strains. Therefore, a demand exists for new antibiotics with broad-spectrum activities that enable them to be prescribed with confidence for empiric monotherapy.

The results of in vitro and in vivo studies indicate that trovafloxacin offers activity comparable to that of ciprofloxacin and ofloxacin against gram-negative respiratory pathogens together with superior activity against gram-positive organisms. Trovafloxacin is also active against the atypical respiratory pathogens. Its extensive activity against pathogens commonly implicated in respiratory infections, together with its ability to achieve concentrations in respiratory tissue far in excess of MICs, suggests that trovafloxacin may provide effective empiric treatment of community- and hospital-acquired infections, including sinusitis, acute exacerbations of chronic bronchitis, community- and hospital-acquired pneumonia, and atypical pneumonia.

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