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Rapid Activity of Finafloxacin in Patients with Urinary Tract Infections and Pyelonephritis Evaluated in Phase 2 Clinical Studies

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Abstract

Background: The novel C-8-cyano fluoroquinolone (FQ) finafloxacin (FINA) was studied in 2 randomized, double-blind, double-dummy phase II clinical trials in patients with uncomplicated or complicated urinary tract infections (uUTI/cUTI) and pyelonephritis (PN) in comparison to ciprofloxacin (CPX).

Methods: Patients with uUTI (n=36) and cUTI/PN (n=225) were enrolled. Pathogen eradication was defined as elimination/reduction of study entry pathogens to $\leq 10^3$ CFU/ml in the urine. For uUTI the primary efficacy endpoint was bacterial eradication at End of Treatment (EoT) on days 4-6. Velocity of eradication was determined in a subset of patients after the first dose. For cUTI/PN early response to FINA/CPX was evaluated in the microbiological intention-to treat population (mITT) at day 3.

Results: 198 baseline uropathogens were isolated from the urine of 193 cUTI/PN mITT patients. 19% were CPX-resistant (CR) pathogens and 8% ESBLs (extended spectrum ß-lactamase).

FINA demonstrated a better early response than CPX, with bacterial eradication rates of

- 89% (n=132) vs 79% (61) in the mITT
- 70% (23) vs 36% (14) in CR-strain infected patients
- 91% (11) vs 0% (3) in ESBL infected patients

FINA was also more active than CPX against pathogens resistant to 12 other, non-FQ antibiotics. Activity of CPX was reduced in patients with acidic urine at screening, whereas FINA-activity remained unaffected.

For uUTI the eradication rate at EoT was 100% for both FINA and CPX in the modified intention-to-treat population. Eradication was achieved by FINA within 2 hrs after in all patients infected with CPX-susceptible strains first dosing and within 8 hrs for a CR strain. CPX eradicated CPX-sensitive strains in one patient each within 2, 4, and 8 hrs.

Conclusion: FINA demonstrated a potent and very rapid activity in cUTI and PN patients, was safe and well tolerated. In contrast to CPX, FINA was not affected by the low urine pH, recorded in most of the patients (80%), and was also clearly more active vs FQ-resistant pathogens. Thus, FINA is a good option for the treatment of uUTI, cUTI and PN with a quick antibacterial activity. It can achieve bacteriological eradication within 2 - 8 hrs after first dosing.

Introduction

- Finafloxacin is a novel, broad spectrum fluoroquinolone (FQ) [1] which is currently undergoing phase II and phase III clinical assessment in different indications.
- Finafloxacin exhibits the unusual property of enhanced *in vitro* and *in vivo* activity at slightly acidic conditions (pH 5.0 – 6.0) under which other marketed FQs show significantly reduced activity [2]. This is also true for anaerobes, adherent [3], slowly growing and intracellular bacteria [4].
- Finafloxacin displays an excellent safety profile in a wide range of predictive, *in vitro*, toxicity assays, *in vivo* animal models and in humans [5].
- Finafloxacin is highly active against bacterial species, like *Burkholderia pseudomallei* and *Burkholderia mallei*, that are able to invade and spread intracellularly within the acidic environment that exists in the organelles of a host, for example, within phagosomes. Diseases caused by these organisms are notoriously difficult to treat.

Here, we present preliminary *in vitro* and *in vivo* data suggesting a potential use of finafloxacin in the treatment of infections in acidic environment.

Methods

Results from two clinical studies with finafloxacin in UTI patients are shown in this presentation:

- A randomized, double-blind, double-dummy, phase II study in 7 centers in Germany and Singapore. 36 female patients between 18 and 55 years with uUTI were randomized to receive either finafloxacin 300 mg b.i.d. or ciprofloxacin 250 mg b.i.d. for 3 days. The primary efficacy endpoint was the bacterial eradication at End of Treatment (EoT) on days 4-6 in both treatment groups defined as the eradication of initial pathogen ($\geq 10^5$ cfu/mL) in urine with no isolation of a new pathogen. In addition the velocity of bacterial killing was determined in a subset of patients by fractionated/two-hourly sampling of urine on the first day of treatment.
- A double-blind, double-dummy phase 2 study at 18 sites in Poland and Germany enrolled 225 patients. Adult patients diagnosed with cUTI and acute PN were randomized to receive finafloxacin (800 mg o.d. i.v. and oral) either for a total of 5 (FINA 5 days) or 10 days (FINA 10 days) or ciprofloxacin (400 mg b.i.d. i.v. or 500 mg b.i.d. oral) for 10 days (CIPRO 10 days) with a potential switch from initial i.v. to oral administration on day 3 or later. The early response to the study medications was evaluated in the mITT at day 3 of the study with pathogen eradication defined as elimination or reduction of study entry pathogens to $\leq 10^3$ CFU/ml in urine culture.
- Susceptibility testing of the isolated pathogens was performed by broth microdilution.

Results

uUTI clinical outcome:

In the modified intention-to-treat population, the eradication rate at End of Treatment was 100% in both treatment groups, 13 out of 13 in the group treated with finafloxacin and 5 out of 5 in the ciprofloxacin arm.

uUTI rapid antibacterial effect:

A subanalysis was performed with 8 patients at the Singapore site (5 finafloxacin , 3 ciprofloxacin). Urine samples were taken pre dose and at 2, 4 and 8 hours after the first dose of study medication for the determination of urinary bacterial counts. Eradication was defined for bacterial counts of $\leq 10^3$ CFU/mL. For all FQ-susceptible pathogens (MICs 0.08 – 0.19 mg/l) bacterial eradication was achieved within with finafloxacin within 2 hours after the initial 300 mg dose (Fig 1). For a patient infected with a highly FQ-resistant *E. coli* (MIC >32 mg/l) eradication was achieved within 8 hours. In comparison, in the ciprofloxacin treatment arm, one patient each reached bacterial eradication at 2 (MIC 0.08 mg/l), 4 (MIC 0.012 mg/l), and 8 hours (MIC 0.19 mg/l) respectively when infected with a ciprofloxacin-susceptible pathogen.

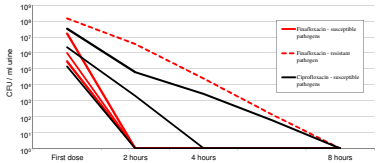

Figure 1 Rapid antibacterial effect of finafloxacin in patients with uUTI

Results

cUTI:

A total of 198 baseline uropathogens were isolated from the urine of 193 patients in the mITT of this phase II study: 81% of the isolated pathogens were *E.coli*, 7% Klebsiella, 2% *P. mirabilis*, and 10 % various pathogens. 19% of the patients in the mITT were infected by CPX-resistant pathogens and 8% produced ESBLs. MIC50 and MIC90 for the predominant species E.coli were 0.06 and 32 for finafloxacin and 0.03 and 32 for ciprofloxacin and 0.5 and 32 for both drugs for the other pathogens (MICs determined at pH 7.2). Resistance profiles for the isolated pathogens are shown in table 1.

Species	FINA 5 days %res (n)	FINA 10 days %res (n)	CIPRO 10 days %res (n)
E. coli (n)	n = 51	n = 51	n = 49
Ciprofloxacin	21.6% (11)	9.8% (5)	22.4% (11)
Nitrofuran	7.5% (4)	9.8% (5)	4.1% (2)
Ampicillin	58.5% (31)	51.0% (26)	55.1% (27)
Trimethoprim-Sulfametaxol	37.7% (20)	25.5% (13)	22.4% (11)
Gentamicin	5.7% (3)	2.0% (1)	6.1% (3)
Co-Amoxiclav	18.9% (10)	11.8% (6)	18.4% (9)
Cefadroxil	13.2% (7)	2.0% (1)	8.2% (4)
Cefepime	1.9% (1)	0% (0)	2.0% (1)
Cefotaxim	13.2% (7)	0% (0)	6.1% (3)
Mecillinam	5.7% (3)	2.0% (1)	6.1% (3)
Piperacillin-Tazobactam	0% (0)	0% (0)	2.0% (1)
Imipenem	0% (0)	0% (0)	0% (0)
Other pathogens (n)	n = 16	n = 10	n = 11
Ciprofloxacin	31.3% (5)	20% (2)	36.4% (4)
Nitrofuran	18.8% (3)	40% (4)	18.2% (2)
Ampicillin	62.5% (10)	60% (6)	63.6% (7)
Trimethoprim-Sulfametaxol	31.3% (5)	40% (4)	18.2% (2)
Gentamicin	18.8% (3)	10% (1)	45.5% (5)
Co-Amoxiclav	31.2% (5)	30% (3)	36.4% (4)
Cefadroxil	25.0% (4)	30% (3)	63.6% (7)
Cefepime	25.0% (4)	0% (0)	27.3% (3)
Cefotaxim	31.2% (5)	20% (2)	45.5% (5)
Mecillinam	43.8% (7)	40% (4)	45.5% (5)
Piperacillin-Tazobactam	25.0% (4)	0% (0)	9.1% (1)
Imipenem	0% (0)	10% (1)	0% (0)

Table 1 Resistance profiles of pathogens isolated in a phase II cUTI study (resistance breakpoints according to CLSI; finafloxacin breakpoint not yet specified)

An evaluation of the microbiological response in patients of the mITT on day 3 of the study indicated that:

- Finafloxacin shows a rapid antibacterial activity and eradicated the pathogens present in the urine in 89% of the patients compared to 79% for ciprofloxacin (Figure 2A).
- Resistance to fluoroquinolones in ESBL producing bacteria in particular causing UTIs is an increasing problem. Finafloxacin also showed a very rapid antimicrobial effect against these pathogens and eradicated ESBLs in 10 out of 11 patients (91%) in the finafloxacin arms of this phase II study. In comparison ciprofloxacin did not show a positive microbiological effect on day 3 in any of the three patients infected with ESBL producers (Figure 2B). This result is consistent with the outcome of a detailed *in vitro* study comparing the activity of finafloxacin and other fluoroquinolones against ESBL producers (see poster A-477 of this conference).
- Finafloxacin demonstrated a better antibacterial activity against ciprofloxacin-resistant pathogens at this early evaluation point (70% for finafloxacin vs. 36% for ciprofloxacin) whereas finafloxacin and ciprofloxacin had similar activity against ciprofloxacin-susceptible pathogens (Figure 2C). 21% of the patients in this study were infected with ciprofloxacin-resistant pathogens.
- The better early eradication was also correlated with the acidic urine found in 80% of the patients in this study (see poster L-1251 at this conference). In consequence, acidic urine further decreased the activity of ciprofloxacin against ciprofloxacin-resistant pathogens whereas finafloxacin activity was preserved under these conditions (Figure 2D).

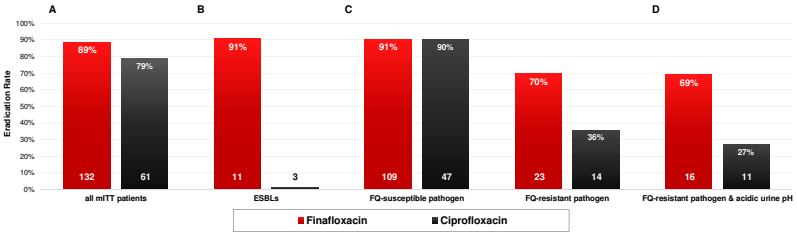

Figure 2 Microbiological outcomes on day 3: **A** all mITT patients, **B** mITT patients with ESBLs and **C** mITT patients with CPX-resistant or –susceptible pathogens **D** at acidic urine pH. Numbers on the bottom of the bars show the numbers of patients.

Finafloxacin demonstrated a potent and rapid antibacterial activity against bacteria isolated at baseline irrespective of whether the bacteria were resistant to fluoroquinolones and/or other antibiotics (Figure 3). In contrast to ciprofloxacin finafloxacin efficiently eradicated pathogens resistant to cephalosporins, imipenem, mecillinam, aminoglycosides, nitrofurantoine and trimethoprim already on day 3 of the ongoing study. The isolated resistant strains in general showed a high level of co-resistance with ciprofloxacin varying from 30% (amoxicillin-resistant pathogens) to 88% (gentamicin-resistant pathogens). Ciprofloxacin especially showed poor activity against such strains whereas finafloxacin maintained it's high activity (data not shown).

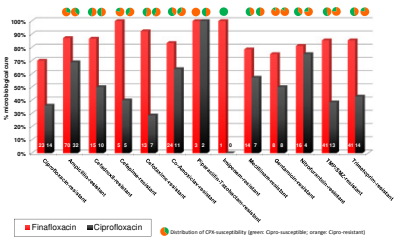

Figure 3 Microbiological outcomes on day 3 for mITT patients with different resistant pathogens. Numbers on the bars show the number of patients.

Conclusions

- Finafloxacin demonstrated a potent and very rapid activity in uUTI, cUTI and pyelonephritis patients. Susceptible pathogens were eradicated within 2 hours, and resistant pathogens within 8 hours by a single 300 mg dose in uUTI patients. Eradication levels in cUTI/pyelonephritis were 89% on day 3 of a 800 mg single daily dosing schedule.
- Finafloxacin demonstrated a rapid and pronounced activity against ESBLs in cUTI/pyelonephritis patients with 91% eradication rate on day 3 of a 800 mg single daily dosing schedule.
- Finafloxacin also showed a rapid high antibacterial activity against ciprofloxacin-resistant pathogens in cUTI/pyelonephritis patients with 70% eradication rate on day 3 of a 800 mg single daily dosing schedule compared to 36% eradication rate achieved by ciprofloxacin .
- In contrast to ciprofloxacin finafloxacin activity was not negatively affected by acidic urine pH prevailing in 80% of the cUTI/pyelonephritis patient population.
- Finafloxacin activity was also not negatively impaired by the resistance of pathogens to chemically not related (classes of) antibacterials, even if it was paired with a ciprofloxacin co-resistance.

Thus, finafloxacin is a viable option for the treatment of uUTI, cUTI and pyelonephritis with a rapid antibacterial activity against a broad range of bacterial pathogens.

Literature

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