Poster # 3566

Clinical and Microbiologic Efficacy of Ciprofloxacin for the Treatment of Uncomplicated Urinary Tract Infections in Adult Women

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ABSTRACT

BACKGROUND: Fluoroquinolones (FQs) remain the most frequently prescribed class of antibiotics for treatment of uncomplicated urinary tract infection (uUTI) even in the face of rising rates of gram negative resistance, exceeding 35% in many communities, and their propensity to cause collateral damage. Despite these concerns, the clinical outcome of patients treated with a FQ who have a non-susceptible pathogen has not been well-studied.

METHODS: An open label study of oral ciprofloxacin 250 mg BID for 3 days in adult women with uUTI was conducted between December 2017 and July 2018 at 20 U.S. sites. Patients with at least two of five classic uUTI symptoms and a positive urine dipstick for both leukocyte esterase and nitrite were enrolled. As defined in the most recent FDA Guidance, a cure is defined as a combination of clinical plus microbiologic cure, without receiving a rescue antibiotic, for patients with a baseline urine culture growing >105 CFU/mL of a uropathogen. Complete resolution of baseline self-reported patient symptoms was used to determine a clinical response of cure. Microbiologic cure required <103 CFU/mL of the baseline pathogen on follow-up culture on Day 12. The test of cure was at Day 12.

RESULTS: 250 adult females (average age 47.3 years) were enrolled of whom 181 met criteria for evaluation. 124/181 (68.5%) patients had a positive baseline urine culture of whom 103/124 (83.1%) was susceptible to FQs and 21/124 (16.9%) non-susceptible. Clinical, microbiologic and overall response for FQ susceptible versus non-susceptible pathogens is shown in the Table.

	Baseline Urinary Pathogen		
	FQ-susceptible	FQ-non-susceptible	p value
Overall Response	**68/103 (66.0%)**	**2/21 (9.5%)**	**<0.001**
Clinical response	75/103 (72.8%)	14/21 (66.7%)	0.5699
Microbiologic response	90/103 (87.4%)	6/21 (28.6%)	<0.001

CONCLUSIONS: Using the FDA's combined endpoint to assess treatment of uUTI, patients infected with FQ non-susceptible uropathogens were significantly less likely to respond to FQ therapy than patients infected with FQ-sensitive strains, driven primarily by a lower microbiologic cure rate. Coupled with recent safety concerns about FQs, the high rate of FQ resistance rates in the community and poor outcome in patients with resistant pathogens underscore the need for better empiric oral treatment options for patients with uUTI.

INTRODUCTION

- Fluoroquinolones (FQs) remain the most frequently prescribed class of antibiotics for treatment of uncomplicated urinary tract infection (uUTI)
- Rates of resistance to quinolones are rising, exceeding 35% in many communities.
- The US Food and Drug Administration has required a warning against the use of quinolones in uncomplicated infections due to safety concerns
- Despite these concerns, the clinical outcome of patients treated with a FQ who have a non-susceptible pathogen has not been well-studied.

METHODS

DESIGN: Multicenter, prospective, non-randomized, open-label trial in U.S.

STUDY PERIOD: December 2017 and July 2018

PATIENTS: Adult women with uncomplicated urinary tract infection having:

- Two of the following signs and symptoms: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain, gross hematuria
- Urinalysis positive for both leucocyte esterase and nitrite
- Without: acute pyelonephritis, recent antibacterial treatment for UTI, predisposing factors for complicated infections (ileal loops, indwelling catheter, paraplegia), pregnancy.

INTERVENTION: Oral ciprofloxacin 250 mg BID for 3 days

PRIMARY ENDPOINT: Per most recent FDA Guidance,

- **Overall cure** is defined as a combination of clinical plus microbiologic cure, without receiving a rescue antibiotic, for patients with a baseline urine culture growing ≥10^5 CFU/mL of a uropathogen.
- **Clinical cure:** Complete resolution of baseline self-reported patient symptoms.
- **Microbiologic cure:** <10^3 CFU/mL of the baseline pathogen on follow-up culture on Day 12.
- **Statistics:** The primary comparison was performed in the Microbiological Modified Intent-to-Treat population on the difference in overall response between patients with a ciprofloxacin susceptible and ciprofloxacin non-susceptible organism at baseline at Day 12. Significance was determined using the Cochran–Mantel–Haenszel test.

RESULTS

Table 1. Baseline Demographics

Characteristic	Susceptible (N = 153)	Non-Susceptible (N = 38)	Other (N=59)	Total (N=250)
Age, years				
Mean (SD)	46.8 (16.8)	50.3 (17.0)	46.7 (15.9)	47.3 (16.0)
Median	45.0	50.5	49.0	46.0
Sex, n (%)				
Female	153 (100.0)	38 (100.0)	59 (100.0)	250 (100.0)
Race, n (%)				
White	128 (83.7)	31 (81.6)	43 (72.9)	202 (80.8)
Black or African American	23 (15.0)	5 (13.2)	14 (23.7)	42 (16.8)
Asian	1 (0.7)	2 (5.3)	1 (1.7)	4 (1.6)
Other	1 (0.7)	0	1 (1.7)	2 (0.8)
Ethnicity, n (%)				
Hispanic/Latino	93 (60.8)	22 (57.9)	32 (54.2)	147 (58.8)
Not Hispanic/Latino	58 (37.9)	16 (42.1)	24 (40.7)	98 (39.2)
Not Reported	2 (1.3)	0	2 (3.4)	4 (1.6)
Unknown	0	0	1 (1.7)	1 (0.4)
BMI, kg/m²				
Mean (SD)	28.62 (7.1)	29.28 (6.4)	29.85 (6.4)	29.01 (6.9)
BMI Distribution				
BMI > 30 kg/m²	54 (35.3)	13 (34.2)	24 (41.4)	91 (36.5)
Diabetes, n (%)	15 (9.8)	4 (10.5)	6 (10.2)	25 (10.0)

RESULTS

Table 2. Summary of Signs and Symptoms of uUTI at Baseline (ITT)

Characteristic	Susceptible	Non-Susceptible	Other	Total
Gross hematuria				
Absent	80/110(72.7)	22/25(88.0)	39/45 (86.7)	141/180 (78.3)
Mild	16/110 (14.5)	2/25 (8.0)	4/45 (8.9)	22/180 (12.2)
Moderate	8/110 (7.3)	1/25 (4.0)	2/45 (4.4)	11/180 (6.1)
Severe	6/110(5.5)	--	--	6/180 (3.3)
Pain/burning with urination				
Absent	15/110(13.6)	1/25 (4.0)	7/45 (15.6)	23/180 (12.8)
Mild	23/110 (20.9)	10/25 (40.0)	5/45 (11.1)	38/180 (21.1)
Moderate	43/110 (39.1)	4/25 (16.0)	15/45 (33.3)	62/180 (34.4)
Severe	29/110 (26.4)	10/25 (40.0)	18/45 (40.0)	57/180 (31.7)
Lower abdominal pain				
Absent	13/110 (11.8)	2/25 (8.0)	6/45 (13.3)	21/180 (11.7)
Mild	14/110 (12.7)	7/25 (28.0)	5/45 (11.1)	26/180 (14.4)
Moderate	62/110 (56.4)	10/25 (40.0)	21/45 (46.7)	93/180 (51.7)
Severe	21/110 (19.1)	6/25 (24.0)	13/45 (28.9)	40/180 (22.2)
Urinary frequency				
Absent	1/69 (1.4)	--	2/37 (5.4)	3/119 (2.5)
Mild	7/69 (10.1)	2/12 (15.4)	4/37 (10.8)	13/119 (10.9)
Moderate	26/69 (37.7)	2/13 (15.4)	6/37 (16.2)	34/119 (28.6)
Severe	35/69 (50.7)	9/13 (69.2)	25/37 (67.6)	69/119 (58.0)
Urinary urgency				
Absent	4/69 (5.8)	1/13 (7.7)	3/37 (8.1)	8/119 (6.7)
Mild	7/69 (10.1)	3/13 (23.1)	2/37 (5.4)	12/119 (10.1)
Moderate	27/69 (39.1)	2/13 (15.4)	9/37 (24.3)	38/119 (10.1)
Severe	31/69 (44.9)	7/13 (53.8)	23/37 (62.2)	61/119 (51.3)
Frequency and urgency				
Absent	1/41 (2.4)	--	--	1/61 (1.6)
Mild	11/41 (26.8)	2/12 (16.7)	3/8 (37.5)	16/61 (26.2)
Moderate	15/41 (36.6)	4/12 (33.3)	2/8 (25.0)	21/61 (34.4)
Severe	14/41 (34.1)	6/12 (50.0)	3/8 (37.5)	23/61 (37.7)

Table 3. Baseline Uropathogens (Micro-MITT Population)

Baseline Pathogens	Susceptible (N=103) n(%)	Non-Susceptible (N=21) n(%)	Total (N=124) n(%)
Number of Subjects with at least one Pathogen at Baseline	103 (100.0)	21 (100.0)	124 (100.0)
Escherichia coli	88 (85.4)	20 (95.2)	108 (87.1)
Klebsiella pneumoniae	10 (9.7)	0	10 (8.1)
Proteus mirabilis	3 (2.9)	0	3 (2.4)
Klebsiella variicola	2 (1.9)	0	2 (1.6)
Enterobacter cloacae	1 (1.0)	1 (4.8)	2 (1.6)
Klebsiella oxytoca	1 (1.0)	0	1 (0.8)
Morganella morganii	1 (1.0)	0	1 (0.8)
Staphylococcus saprophyticus	1 (1.0)	0	1 (0.8)

Table 4. Response at Test of Cure (Day 12) in m-MITT Population

Overall Response	Susceptible N = 103	Non-susceptible N = 21	P value
Responder	68 (66.0)	2 (9.5)	<0.001
Non-responder	34 (33.0)	18 (85.7)	
Indeterminate	1 (1.0)	1 (4.8)	
Reasons for Non-response			
Baseline symptoms of uUTI not resolved	25 (24.3)	6 (28.6)	
TOC urine culture + for ≥ 10^3 CFU of baseline pathogen	13 (12.6)	14 (66.7)	
Received new non-study antibacterial therapy	9 (8.7)	7 (33.3)	
Clinical Response	**N = 103**	**N = 21**	
Cure	75 (72.8)	14 (66.7)	0.570
Failure	27 (26.2)	6 (28.6)	
Indeterminate	1 (1.0)	1 (4.8)	
Microbiologic Response	**N = 103**	**N = 21**	
Eradication	90 (87.4)	6 (28.6)	<0.001
Persistence	13 (12.6)	14 (66.7)	
Indeterminate	--	1 (4.8)	
Investigator Response	**N = 103**	**N = 20**	
Clinical Cure	97 (94.2)	16 (80.0)	0.035
Clinical Failure	5 (4.9)	2 (10.0)	
Indeterminate	1 (1.0)	2 (10.0)	

Table 5. Microbiologic Response at Test of Cure (m-MITT)

Baseline Pathogen	Susceptible	Non-susceptible
Escherichia coli	77/88 (87.5)	5/18 (27.8)
Klebsiella spp.	11/13 (84.6)	--
K. oxytoca	1/1 (100.0)	--
K. pneumoniae	8/10 (80.0)	--
K. variicola	2/2 (100.0)	--
Proteus mirabilis	3/3 (100.0)	--

Table 6. Summary of Treatment-Emergent Adverse Events

TEAE Category	Susceptible (N = 150)	Non-Susceptible (N = 37)	Other (N=57)
No. (%) of subjects with any:			
TEAE	20 (13.3)	3 (8.1)	4 (7.0)
Drug-Related TEAE	5 (3.3)	--	3 (5.7)
Serious TEAE	--	--	--
TEAE leading to premature discontinuation of study drug	--	--	1 (1.8)

CONCLUSIONS

- 17% (21/124)of patients had a quinolone resistant organism at baseline
- Quinolone resistance was associated with a significantly higher rate of treatment failure
  - Driven primarily by a lower microbiologic cure rate
  - Symptoms tend to improve over time
- The high rate of FQ resistance rates in the community and poor outcome in patients with resistant pathogens underscore the need for better empiric oral treatment options for patients with uUTI and better diagnostic tests.

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