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Comparative Fidaxomicin Susceptibilities of Isolates Collected at Baseline, Failure, and Recurrence From Subjects in a Phase 3 Trial of *Clostridium difficile* Infection (CDI)

E.J.C. GOLDSTEIN,[1] D.M. CITRON,[1] P. SEARS,[2] F. BABAKHANI,[2] and D.N. GERDING[3]

[1]R.M. Alden Research Laboratory, Culver City, CA; [2]Optimer Pharmaceuticals, San Diego, CA; [3]Hines VA Hospital, Chicago, IL

Abstract

BACKGROUND A 10-day course of oral fidaxomicin (FDX; formerly OPT-80; 200 mg bid), a potent new macrocyclic antibiotic, was compared with vancomycin (VAN; 125 mg qid) in 629 adults (548 evaluable) with CDI in a phase 3 randomized, double-blind trial at sites across North America.

METHODS Fecal specimens were collected from subjects at study entry and at failure or recurrence and cultured for *C difficile*. Antimicrobial susceptibilities of FDX, VAN, metronidazole (MTZ), and rifaximin (RFX) were determined using the CLSI reference method. Isolates were genotyped via restriction endonuclease analysis (REA) methods.

RESULTS Susceptibility (MIC_{90}) of baseline isolates did not predict clinical cure, failure, or recurrence for either FDX (MIC_{90}, 0.25 µg/mL) or VAN (MIC_{90}, 2 µg/mL). Of 10 failures in the mITT group (8 VAN and 2 FDX) with strains isolated at baseline and end of therapy, both FDX isolates were the same but 2 VAN were different REA types. Of 47 subjects with baseline and recurrence samples, 2/14 (14%) FDX and 6/33 (19%) VAN subjects had new strains at recurrence. There were no geographic differences in susceptibilities, except for RFX, where US MIC_{90} was > 256 µg/mL compared with Canada MIC_{90}, 0.03 µg/mL. All RFX resistant isolates were from the US. No differences were present between the $MIC_{50/90}$ of subjects admitted as MTZ failures and those who were not.

CONCLUSIONS There was no relationship between the MIC of baseline clinical isolates and clinical outcome. No resistance to either FDX or VAN developed during the study. MIC_{90}s were generally low (0.25 µg/mL for FDX and 2 µg/mL for VAN) and were not different in different REA groups, except that 24/166 (14%) of BI and 3/17 (18%) of K group strains were RFX resistant, and MTZ susceptibilities were also lower in these groups.

Introduction

Clostridium difficile infection (CDI) has become an increasingly common and more serious threat to subjects in the hospital and the community. The emergence of a new and more potent toxin-producing epidemic strain (known as 027/BI/NAP1) resulted in increased mortality of hospitalized subjects, many of whom were elderly. Its initial presentation often went unrecognized until the subject was toxic and had an elevated white blood cell (WBC) count and a marked ileus. Typical current treatment of CDI has been metronidazole for mild to moderate infection and vancomycin for more serious infection. It has been shown that response to therapy with metronidazole is not as good as that with vancomycin,[1] but guidelines suggest the use of vancomycin only with serious infections and relapses because of the potential for emergence of vancomycin-resistant enterococci (VRE) and, more recently, of decreased *Staphylococcus aureus* susceptibilities (MIC creep). In addition, response to these therapies is often slow, and relapse occurs in approximately 20% of subjects.[2] Consequently, there is an unmet medical need for the development of more efficacious drugs, especially in other classes, that would allow targeted and improved clinical response.

Fidaxomicin (formerly OPT-80, PAR-101) is a potent new macrocyclic antibiotic with a narrow spectrum of activity, with limited activity against gram-negative bacteria and most anaerobes but high activity against *C difficile*. It targets RNA polymerase, has a high concentration in the gut, and has minimal systemic absorption. Against 110 toxogenic strains, Hecht et al[3] found fidaxomicin had an MIC_{90} of 0.125 µg/mL compared with 0.5 and 2 µg/mL for metronidazole and vancomycin, respectively.

We report on the comparative fidaxomicin susceptibilities of isolates collected at baseline, failure, and recurrence from subjects in a phase 3 trial of CDI.

Materials and Methods

In a phase 3 randomized, double-blind trial of a 10-day course of treatment, oral fidaxomicin (FDX; 200 mg bid), a potent new macrocyclic antibiotic, was compared with vancomycin (VAN; 125 mg qid) in 629 adults (548 evaluable) with CDI at sites across North America (US and Canada). Subjects with mild to moderate *C difficile*, males and females aged ≥ 16 years with > 3 diarrheal (liquid or unformed) stools/day and with a positive enzyme immunoassay for *C difficile* toxin or cell cytotoxicity assay and no more than 24 hours of prior treatment for *C difficile* were eligible for enrollment. Only subjects with a primary episode or first relapse of disease were eligible. Metronidazole but not vancomycin failures were eligible for enrollment. Subjects with ileus, WBC > 30 × 10^9/L, toxic megacolon, or concern about life-threatening CDI were excluded from study entry. Subjects with severe underlying disease who were not expected to survive for 72 hours regardless of cause, who had had more than a single occurrence within 3 months, or who had Crohn's disease or ulcerative colitis were also excluded. Subjects were randomized to receive either fidaxomicin 200 mg orally twice daily or vancomycin 125 mg orally four times daily for 10 days. They were evaluated for clinical cure at end of therapy and relapse out to 4 weeks following the end of treatment.

Stool samples were collected at entry (baseline) and at treatment failure or recurrence, where appropriate. *C difficile* strains were isolated from stool on cycloserine-cefoxitin fructose agar in an anaerobic chamber. Colonies with typical *C difficile* morphology were subcultured on supplemented (hemin, vitamin K_1) brucella agar and their identity confirmed via colony morphology, Gram stain, and a positive proline test result. Susceptibility of isolates against fidaxomicin, vancomycin, metronidazole, and rifaximin were determined via Clinical and Laboratory Standards Institute agar dilution methods. *C difficile* typing was performed via restriction endonuclease analysis (REA) by the method of Clabots et al.[4]

Results

Susceptibility (MIC_{90}) of baseline isolates did not predict clinical cure, failure, or recurrence for either FDX (MIC_{90}, 0.25 µg/mL) or VAN (MIC_{90}, 2 µg/mL) (Tables 1 and 2). Of 10 failures in the modified intent to treat (mITT) group (8 VAN and 2 FDX) with strains isolated at baseline and end of therapy, both FDX isolates were the same but 2 VAN were different REA types (Table 3). Of 47 subjects with baseline and recurrence samples, 2 of 14 (14%) FDX and 6 of 33 (19%) VAN subjects had new strains at recurrence. No shifts in susceptibility were noted between baseline and failure or recurrence, except for 1 untypable strain that showed a decrease in FDX MIC from 0.125 µg/mL at baseline to 0.015 µg/mL at recurrence. MIC_{90}s were generally low (0.25 µg/mL for FDX and 2 µg/mL for VAN) and were not different in different REA groups, except that 24/166 (14%) of BI and 3/17 (18%) of K group strains were RFX resistant, and MTZ susceptibilities were also lower in these groups (Table 3). There were no geographic differences (Figure 1) in susceptibilities, except for rifaximin, where overall US MIC_{90} was > 256 µg/mL compared with Canada (MIC_{90}, 0.03 µg/mL). All rifaximin-resistant isolates were from the US. No differences were present between the $MIC_{50/90}$ of subjects admitted as metronidazole failures and those who were not (Table 4).

Table 1. Summary of Susceptibility of Baseline Isolates by Treatment Group and Antibiotic Primary Clinical Outcome of Cure (per protocol population)

Treatment Group	N	Antibiotic	Geometric Mean (range)	MIC_{50}, µg/mL	MIC_{90}, 027/BI/NAP1, µg/mL
Fidaxomicin					
Cure	244	Fidaxomicin	0.09 (0.007–0.5)	0.125	0.25
Failure	21	Fidaxomicin	0.13 (0.03–0.25)	0.125	0.25
Vancomycin					
Cure	254	Vancomycin	0.80 (0.25–4.0)	1	2
Failure	29	Vancomycin	0.84 (0.5–2.0)	1	2

MIC = minimum inhibitory concentration.

Table 2. Summary of Susceptibility of Baseline Isolates by Treatment Group and Antibiotic Secondary Clinical Outcome of Recurrence (per protocol population)

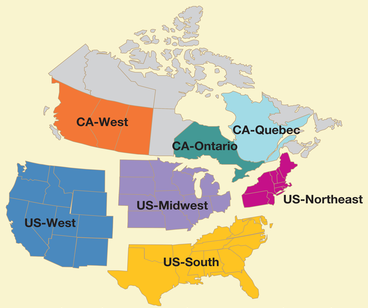
Treatment Group	N	Antibiotic	Geometric Mean (Range)	MIC_{50}, µg/mL	MIC_{90}, µg/mL
Fidaxomicin					
Nonrecurrence	183	Fidaxomicin	0.08 (0.007-0.5)	0.125	0.25
Recurrence	28	Fidaxomicin	0.11 (0.015-0.5)	0.125	0.25
Vancomycin					
Nonrecurrence	168	Vancomycin	0.77 (0.25-4.0)	0.5	2
Recurrence	53	Vancomycin	0.80 (0.25-4.0)	1	2

Table 3. Susceptibility Profiles of REA Groups Isolated at Baseline (modified intent-to-treat population)

REA Group	N	Antibiotic	Geometric Mean (Range)	MIC_{50}, µg/mL	MIC_{90}, µg/mL
BI	158	Fidaxomicin	0.16 (0.015-0.5)	0.25	0.25
		Vancomycin	0.88 (0.5-4)	1	2
		Metronidazole	0.86 (0.125-4)	1	2
		Rifaximin	0.07 (0.004-257)	0.015	257
BK	2	Fidaxomicin	0.09 (0.06-0.125)	0.06	0.125
		Vancomycin	1 (1-1)	1	1
		Metronidazole	0.5 (0.5-0.5)	0.5	0.5
		Rifaximin	0.02 (0.015-0.015)	0.015	0.015
CF	3	Fidaxomicin	0.09 (0.03-0.25)	0.06	0.25
		Vancomycin	0.71 (0.5-1)	0.5	1
		Metronidazole	0.42 (0.125-1)	0.5	1
		Rifaximin	0.01 (0.008-0.015)	0.008	0.015
G	30	Fidaxomicin	0.08 (0.015-0.25)	0.06	0.125
		Vancomycin	0.75 (0.5-2)	0.5	2
		Metronidazole	0.31 (0.125-0.5)	0.25	0.5
		Rifaximin	0.01 (0.003-0.125)	0.008	0.06
J	24	Fidaxomicin	0.03 (0.007-0.125)	0.03	0.06
		Vancomycin	0.69 (0.5-2)	0.5	1
		Metronidazole	0.35 (0.125-2)	0.25	1
		Rifaximin	0.02 (0.008-257)	0.015	0.06
K	17	Fidaxomicin	0.07 (0.015-0.25)	0.06	0.125
		Vancomycin	1.04 (0.5-4)	1	2
		Metronidazole	0.66 (0.125-4)	0.5	2
		Rifaximin	0.18 (0.004-257)	0.015	257
L	1	Fidaxomicin	0.13 (0.125-0.125)	0.125	0.125
		Vancomycin	0.5 (0.5-0.5)	0.5	0.5
		Metronidazole	0.5 (0.5-0.5)	0.5	0.5
		Rifaximin	0.13 (0.125-0.125)	0.125	0.125
Nonsp REA	148	Fidaxomicin	0.08 (0.003-0.5)	0.06	0.125
		Vancomycin	0.77 (0.25-2)	1	2
		Metronidazole	0.30 (0.02-2)	0.25	0.5
		Rifaximin	0.02 (0.003-257)	0.015	0.06
Y	32	Fidaxomicin	0.07 (0.015-0.25)	0.06	0.125
		Vancomycin	0.65 (0.25-4)	0.5	1
		Metronidazole	0.32 (0.06-1)	0.25	0.5
		Rifaximin	0.01 (0.003-257)	0.008	0.03
All strains	415	Fidaxomicin	0.10 (0.003-0.5)	0.125	0.25
		Vancomycin	0.80 (0.25-4)	1	2
		Metronidazole	0.47 (0.02-4)	0.5	1
		Rifaximin	0.03 (0.003-257)	0.015	0.125

REA = restriction endonuclease analysis; Nonsp = nonspecific.

Figure 1. Summary of susceptibility of baseline isolates by treatment group, geographic region, and antibiotic (per protocol population).[a]



Geographic Region	N	Antibiotic	Geometric Mean (Range)	MIC_{50}, µg/mL	MIC_{90}, µg/mL
CA-Ontario	37	Fidaxomicin	0.09 (0.007-0.25)	0.125	0.25
		Vancomycin	0.86 (0.5-1)	1	1
		Metronidazole	0.72 (0.125-4)	1	2
		Rifaximin	0.01 (0.003-0.03)	0.015	0.015
CA-Quebec	96	Fidaxomicin	0.10 (0.015-0.5)	0.125	0.25
		Vancomycin	0.83 (0.5-4)	1	2
		Metronidazole	0.44 (0.06-4)	0.5	1
		Rifaximin	0.01 (0.003-0.06)	0.015	0.015
CA-West	98	Fidaxomicin	0.07 (0.007-0.5)	0.06	0.25
		Vancomycin	0.72 (0.25-2)	0.5	1
		Metronidazole	0.28 (0.02-2)	0.25	0.5
		Rifaximin	0.01 (0.003-0.125)	0.008	0.06
US-Midwest	136	Fidaxomicin	0.11 (0.007-0.5)	0.125	0.25
		Vancomycin	0.81 (0.25-4)	0.5	2
		Metronidazole	0.52 (0.125-2)	0.5	1
		Rifaximin	0.06 (0.003-257)	0.015	257
US-Northeast	53	Fidaxomicin	0.12 (0.003-0.5)	0.125	0.25
		Vancomycin	1.03 (0.5-2)	1	2
		Metronidazole	0.84 (0.25-2)	1	2
		Rifaximin	0.47 (0.008-257)	0.03	257
US-South	83	Fidaxomicin	0.11 (0.015-0.5)	0.125	0.25
		Vancomycin	0.78 (0.25-4)	0.5	2
		Metronidazole	0.53 (0.125-4)	0.5	1
		Rifaximin	0.03 (0.004-257)	0.015	0.125
US-West	45	Fidaxomicin	0.06 (0.003-0.25)	0.06	0.125
		Vancomycin	0.83 (0.25-2)	1	2
		Metronidazole	0.49 (0.125-2)	0.5	2
		Rifaximin	0.21 (0.008-257)	0.015	257

CA = Canada; US = United States.
[a]Overall results from fidaxomicin and vancomycin groups.

Table 4. Characteristics of Strains From Subjects Who Enrolled as Metronidazole Failures (per protocol population)[a]

Metronidazole Failure	N	Antibiotic	Geometric Mean (Range)	MIC_{50}, µg/mL	MIC_{90}, µg/mL
Yes	29	Fidaxomicin	0.10 (0.03-0.25)	0.125	0.25
		Vancomycin	0.83 (0.25-2)	1	2
		Metronidazole	0.39 (0.125-1)	0.25	1
		Rifaximin	0.03 (0.004-257)	0.015	0.06
No	519	Fidaxomicin	0.09 (0.003-0.5)	0.125	0.25
		Vancomycin	0.80 (0.25-4)	1	2
		Metronidazole	0.46 (0.02-4)	0.5	1
		Rifaximin	0.03 (0.003-257)	0.015	0.125

MIC = minimum inhibitory concentration.
[a]Overall results from fidaxomicin and vancomycin groups.

Conclusions

There were no differences between the MIC_{50} and MIC_{90} of baseline clinical isolates and clinical outcome. Fidaxomicin and vancomycin MICs were generally the same for failures and cures (Table 1, per protocol population).

Likewise, there were no notable differences in MIC_{50} and MIC_{90} for cognate antibiotics between recurrences and nonrecurrences (Table 2, per protocol population).

MIC_{90}s were generally low (0.25 µg/mL for fidaxomicin and 2 µg/mL for vancomycin) and were not different in different REA groups, except that 24/166 (14%) of BI and 3/17 (18%) of K group strains were rifaximin resistant, and metronidazole susceptibilities were also lower in these groups.

No notable differences in susceptibility of isolates were detected between the different geographic regions (Figure 1), except that there was more rifaximin resistance in the United States (MIC_{90} > 256 µg/mL) than in Canada (MIC_{90} 0.03 µg/mL), where rifaximin is not licensed.

There were no differences in MIC_{50} and MIC_{90} values of strains for any antibiotic, including metronidazole, even if the subject was enrolled as a metronidazole failure.

Of those subjects with strains isolated at baseline and failure, or at baseline and recurrence, both fidaxomicin failures and 6 of 8 vancomycin failures had the same strain type at baseline and at failure. Six of 33 of the vancomycin-treated subjects and 2 of 14 of the fidaxomicin-treated subjects had a new strain isolated at recurrence compared with baseline.

Fidaxomicin MIC values were low at baseline, and resistance did not develop during the clinical trial.

References

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