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Randomized Clinical Trial (RCT) in *Clostridium difficile* Infection (CDI) Confirms Equivalent Cure Rate and Lower Recurrence Rate of Fidaxomicin (FDX) versus Vancomycin (VCN)

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Abstract

OBJECTIVES CDI is a severe diarrhoeal disease that is usually treated with oral vancomycin or metronidazole. While cure rates are generally 85-90%, recurrences are problematic, 20-30% with either drug. This phase 3, non-inferiority RCT was designed to compare efficacy and safety of oral FDX with oral VCN in patients with confirmed CDI. FDX, a first-in-class macrocyclic antibiotic, is bactericidal and has a prolonged post-antibiotic effect (10 h). It does not perturb the fecal flora.

METHODS Eligible patients were adults with acute CDI symptoms and a positive stool toxin test. Patients received oral FDX (200 mg twice daily) or oral VCN (125 mg 4 times daily) for 10 days. Primary end point was clinical cure (resolution of symptoms and no further need for CDI therapy). Secondary end points were CDI recurrence (diarrhoea and positive stool toxin test within 4 weeks after treatment) and global cure (clinical cure with no recurrence).

RESULTS 535 subjects were randomized, of whom 524 were available for safety, 509 for modified intent-to-treat (mITT) and 451 for per protocol (PP) analyses. 100 clinical sites from Europe (39%), USA (30%) and Canada (31%) contributed subjects. Mean age was 63.4 yr; 60.9% were female. The trial met the primary end point of non-inferiority with 91.7% cured vs 90.6% (FDX vs VCN, respectively, PP population). Recurrence was seen in 12.8% vs 25.3% (FDX vs VCN, respectively, PP, $P = 0.002$). Global cure was noted in 79.6% vs 65.5% (FDX vs VCN, respectively, PP, $P < 0.001$). In all instances PP and mITT analyses were similar. FDX was well tolerated with an adverse event profile similar to that of VCN.

CONCLUSION In this second phase 3 trial of FDX vs VCN, similar results were found with equivalent cure rates, but significantly lower recurrence rates and higher global cures for FDX. With over 1100 subjects enrolled in these 2 RCTs, both showing similar results, FDX offers potential advantages over existing therapies as a single agent that can provide a high cure rate and fewer recurrences.

Introduction

- *Clostridium difficile* infection (CDI), also known as *C difficile*–associated diarrhea, generally occurs after exposure to broad-spectrum antibiotics
  - The incidence and severity of CDI are increasing
  - These increases have been ascribed to the emergence of a hypervirulent *C difficile* strain that is resistant to fluoroquinolones, known variously as North American Pulsed Field type 1 (NAP1), restriction endonuclease analysis type BI, or polymerase chain reaction ribotype 027
  - CDI-associated mortality rates are rising, and CDI is occurring in populations previously considered at low risk, such as young, healthy persons and peripartum women
  - Compared with earlier observations, clinical response and recurrence rates have become more problematic in recent studies
- Fidaxomicin (FDX, previously referred to as OPT-80), a first-in-class macrocyclic antibiotic, is approximately 8-fold more active than vancomycin (VCN) in vitro against clinical isolates of *C difficile*, including NAP1/BI/027 strains
  - This activity, in combination with minimal systemic absorption, high fecal concentrations, prolonged postantibiotic effect (~10 hours), and limited in vitro and in vivo activity against normal gut flora, makes FDX a promising candidate and provides highly active but more selective therapy for CDI
  - A similarly designed phase 3 trial comparing FDX with VCN was presented at ECCMID 2009 and showed favorable outcomes—lower recurrence rates and higher global cure rates—for FDX; this trial was restricted to sites in North America
- Presented here are the results of a second prospective, randomized, double-blind, phase 3, noninferiority study combining sites from Europe (39%), Canada (31%), and the United States (30%)

Methods

- This was a randomized, double-blind trial comparing the safety and efficacy of FDX with those of VCN
- Subjects had to have met inclusion and exclusion criteria and to have received diagnoses of CDI
- They were further stratified by
  - First CDI episode
  - First recurrence of CDI in the past 3 months
- Subjects were randomly assigned at each site to receive FDX (by mouth [PO] 200 mg every 12 hours) or VCN (PO 125 mg every 6 hours), packaged for blinding into 4 doses per day
- Subjects were evaluated clinically during the 10-day course of therapy for cure or failure
  - If cured, subjects were followed up for recurrence for 28 ± 2 days after the last dose of study medication
  - Clinical responses (cure/failure, recurrence) were based on the investigator's assessment of clinical parameters, the most important of which was resolution of diarrhea
  - Assays for toxins A and B were performed at the early termination visit for subjects whose treatment failed
- Subjects were further evaluated for changes in the number and character of stools and for other signs and symptoms or laboratory values indicative of CDI
- Subjects who were cured were evaluated for diarrhea during posttherapy follow-up until study days 36 to 40 (poststudy visit). Subjects with recurring diarrhea were evaluated for the presence of toxins A and B
- Coadministration of any oral or parenteral antibacterials was captured up to the poststudy visit (days 36-40)
- All subjects in the primary analysis were evaluated for global cure (defined as cure without recurrence at any time until the poststudy visit)
- All efficacy analyses were performed on the modified intent-to-treat (mITT [subjects who received at least 1 dose of treatment]) and the per-protocol (PP [subjects who received treatment for at least 8 days of the 10-day course]) populations
- The primary analysis of the noninferiority of cure was conducted on the PP population
  - A gatekeeping strategy was used as the adjustment method to maintain the overall family error rate for assessing superiority of recurrence and global cure between treatment groups in both populations

Results

- As shown in **Table 1**, 535 subjects were randomly assigned, and 85.3% completed therapy

Table 1. Disposition

	FDX, n	VCN, n	Total, n
Randomly assigned	270	265	535
Randomly assigned and received study drug	264	260	524
Completed end of therapy	225	231	456
Completed follow-up period	227	221	448

535 subjects were enrolled.

- **Table 2** shows the number of subjects in the mITT and PP analyses for cure and recurrence

Table 2. Analysis Populations

	FDX, n	VCN, n	Total, n
Safety	264	260	524
mITT (cure and global cure)	252	257	509
PP (cure and global cure)	216	235	451
mITT2 (recurrence)	221	223	444
PP2 (recurrence)	180	182	362

- Baseline characteristics are shown in **Table 3**. No notable differences were observed between the treatment groups

Table 3. Demographics/Baseline Characteristics (mITT)

	FDX	VCN	Total
Age, y, mean ± SD	64.3 ± 17.9	62.5 ± 18.4	63.4 ± 18.1
Age ≥65 y, %	56.3	51.0	53.6
Female, %	58.7	63.0	60.9
White, %	92.1	92.6	92.3
Inpatient, %	69.0	67.3	68.2
No previous episode, %	84.1	86.0	85.1
UBMs 24 h before CDI treatment, n, mean ± SD	7.5 ± 4.4	7.4 ± 4.4	7.5 ± 4.4
CDI indication—diarrhea alone, %	74.6	74.7	74.7
Previous CDI antibiotic use, %	89.3	85.6	87.4
Metronidazole failure, %	4.8	3.1	3.9

UBMs, unformed bowel movements.

- The primary end point of noninferiority for cure was met (**Table 4**). mITT and PP analyses showed no significant difference in cure rates for both drugs

Table 4. Cure Rates (Primary End Point)

Analysis Population	FDX, n/Total (%) (95% CI)	VCN, n/Total (%) (95% CI)	Difference, % (95% CI)
mITT	221/252 (87.7) (83.0, 91.2)	223/257 (86.8) (82.0, 90.4)	0.9 (–4.9, 6.7)
PP	198/216 (91.7) (87.1, 94.7)	213/235 (90.6) (86.1, 93.8)	1.0 (–4.3, 6.3)

CI, confidence interval.
Of the 535 randomly assigned subjects, 509 were included in the efficacy analysis.
Final nonevaluability rate, 15.7%.

- mITT and PP analyses revealed that recurrence rates were significantly lower with FDX than with VCN (**Table 5**)
  - The mITT recurrence rate decreased from 26.9% with VCN to 12.7% with FDX, a 53% relative reduction
  - The PP recurrence rate was 25.3% for VCN and 12.8% for FDX, a 49% relative reduction

Table 5. Recurrence Rates (Secondary End Point)

Analysis Population	FDX, n/Total (%) (95% CI)	VCN, n/Total (%) (95% CI)	Difference, % (95% CI) *P*
mITT	28/221 (12.7) (8.9, 17.8)	60/223 (26.9) (21.5, 33.1)	–14.2 (–21.4, –6.8) <0.001
PP	23/180 (12.8) (8.6, 18.5)	46/182 (25.3) (19.5, 32.1)	–12.5 (–20.3, –4.4) 0.002

CI, confidence interval.

- Global cure (cure at end of treatment without relapse within 28 days) rates were significantly higher with FDX than with VCN (**Table 6**)
  - In the mITT population, 76.6% of subjects receiving FDX achieved global cure compared with 63.4% of subjects receiving VCN
  - In the PP population, 79.6% of subjects receiving FDX achieved global cure compared with 65.5% of subjects receiving VCN

Table 6. Global Cure Rates (Secondary End Point)

Analysis Population	FDX, n/Total (%) (95% CI)	VCN, n/Total (%) (95% CI)	Difference, % (95% CI) *P*
mITT	193/252 (76.6) (71.0, 81.4)	163/257 (63.4) (57.4, 69.1)	13.2 (5.2, 20.9) 0.001
PP	172/216 (79.6) (73.7, 84.5)	154/235 (65.5) (59.2, 71.3)	14.1 (5.9, 22.1) <0.001

CI, confidence interval.

- Treatment-emergent adverse events (AEs) were similar for both arms; 1 AE (in the VCN arm) was definitely ascribed to treatment (**Table 7**)

Table 7. Overall Safety: Adverse Events

	FDX, %	VCN, %
Overall AEs	70.5	68.1
Moderate	21.2	18.5
Severe	19.7	16.2
Possibly related	11.7	13.5
Definitely related	0.0	0.4
Overall SAEs	26.5	22.3

- Serious adverse events (SAEs) were uncommon and similar in both treatment arms (**Table 8**). A single case of torsade de pointes was identified, and it occurred in the VCN arm

Table 8. SAEs Occurring in ≥4 Subjects Receiving FDX

	FDX, n (%)	VCN, n (%)
C difficile colitis	5 (1.9)	3 (1.2)
Pneumonia	4 (1.5)	5 (1.9)
Sepsis	4 (1.5)	2 (0.8)
Hyponatremia	4 (1.5)	0 (0.0)
Neutropenia	4 (1.5)	0 (0.0)
Myocardial infarction	4 (1.5)	0 (0.0)

- The NAP1/BI/027 strain was identified in 32% of subjects (**Table 9**)
  - For cure, there was no difference in response to FDX or VCN
  - Cure rates for the NAP1/BI/027 strain trended lower than did cure rates for the non-NAP1/BI/027 strain in the mITT and PP analyses
  - Recurrence rates were lower for those treated with FDX than for those treated with VCN in the NAP1/BI/027 and non-NAP1/BI/027 groups for mITT and PP analyses
  - Similarly, global cure rates were higher in those treated with FDX than in those treated with VCN in the NAP1/BI/027 and non-NAP1/BI/027 groups for mITT and PP analyses

Table 9. Occurrence of NAP1/BI/027 Strains in the mITT Population

	Subjects, n/Total (%)		
Initial Strain of CDI	FDX	VCN	χ^2_1, (*P*)
Cure			
NAP1/BI/027	54/65 (83.1)	47/57 (82.5)	0.01 (0.928)
Non-NAP1/BI/027	120/131 (91.6)	108/123 (87.8)	1.00 (0.318)
Recurrence			
NAP1/BI/027	12/54 (22.2)	18/47 (38.3)	3.11 (0.078)
Non-NAP1/BI/027	11/120 (9.2)	30/108 (27.8)	13.35 (0.001)
Global Cure			
NAP1/BI/027	42/65 (64.6)	29/57 (50.9)	2.36 (0.125)
Non-NAP1/BI/027	109/131 (83.2)	78/123 (63.4)	12.80 (0.001)

χ^2_1 = chi-square with 1 degree of freedom.

- Results calculated for PP were similar to those for mITT.

Comparison of First Trial (003) and Second Trial (004) (total, ~1100 subjects)

- High level of consistency between the results of both trials
  - Clinical data extremely robust
- Primary outcome of noninferiority for cure met
- Significantly lower recurrence rates for FDX
- Significantly higher global cure rates for FDX
- No safety questions or signals in either trial
- NAP1/BI/027 strain identified in 36% of 003 and 32% of 004 patients with evaluable strain types
  - Reduced relapse rates and higher global cure rates were seen with FDX compared with VCN in 004, similar to what was seen in 003

Conclusions

- FDX has a cure rate for *C difficile* infection equivalent to that of VCN
- FDX results in fewer relapses of *C difficile* infection than VCN, leading to a higher global cure rate
- FDX and VCN have similar reduced cure rates for NAP1/BI/027 strains, but FDX may have a better global cure rate and fewer recurrences
- FDX produces minor perturbation to the bowel flora
- FDX has few systemic adverse events, similar to oral VCN
- FDX offers potential advantages over current therapies for *C difficile* infection

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