Poster #420

ABSTRACT

Background: A phase 3 trial of fidaxomicin (FDX; formerly OPT-80) vs. vancomycin (VAN) for treatment of *Clostridium difficile* infection (CDI) has been used to determine if certain patient factors are able to predict clinical cure (CC), relapse (REL) and global cure (GC; total of CC + no REL) rates for this disease.

Methods: The database of the phase 3 trial was analyzed for impact of patient age, albumin, and WBC/fever at time of CDI diagnosis on CC, REL, and GC rates. FDX and VAN treatment groups in the mITT study population were combined for this analysis.

Results: 629 patients were enrolled into the study, of whom 596 (mITT group) were analyzed. There was a significant correlation or strong trend between age, albumin and strain type with all 3 outcomes, while WBC/fever only correlated with CC and GC but not with the REL rate.

Conclusions: In the FDX/VAN trial, advanced patient age, low albumin levels and strain type were correlated with poor outcomes for all 3 endpoints, while high WBC/fever affected CC and GC but not the REL rate. These data may be useful to create a simplified scoring system to evaluate CDI therapies and clinical outcomes.

Age, Serum Albumin, and Leukocytosis/Fever Predict Clinical Outcomes of *Clostridium difficile* Infection Treated with Fidaxomicin and Vancomycin

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Background

Clostridium difficile infection (CDI) is the most common cause of healthcare-associated infectious nosocomial diarrhea. It is believed that development of symptomatic CDI involves a complex interplay between

- contact with a pathogenic and toxigenic strain of *C. difficile*
- development of intestinal colonization with this strain
- modification of normal intestinal flora (e.g. antibiotics, intestinal surgery)
- production of C. difficile toxins
- susceptibility of the host by yet-to-be-determined immunologic factors

Despite many epidemiologic analyses of CDI, a simplified and validated risk index has yet to be developed which can reliably predict:

- cure of CDI at end of usual therapy
- relapse of CDI within 28 days of end of usual therapy
- serious morbidity related to CDI (i.e. ICU admission, colectomy)
- mortality related to CDI

Fidaxomicin (FDX), formerly known as OPT-80, a novel antibacterial agent in the macrocyclic class, targets bacterial RNA polymerase and is extremely potent against all strains of *C. difficile*.[1]

The recently-presented results of the North American Phase 3 clinical trial of fidaxomicin vs. vancomycin (VAN) for the treatment of CDI showed that fidaxomicin was non-inferior to vancomycin for cure of CDI at end-of-therapy. However, fidaxomicin therapy was associated with a statistically and clinically significant reduction in relapse rate and global cure rate (cure plus no relapse) following CDI treatment.[2,3]

The results of the North American Phase 3 fidaxomicin/vancomycin trial were used to assess the relative importance of readily-available "bedside" clinical and laboratory variables to predict clinical cure (CC), relapse (REL) within 28 days of end of therapy, and global cure (GC = cure plus no relapse).

Methods

The study was a Phase 3, randomized, double-blind, comparative clinical trial of FDX 200 mg orally BID vs. VAN 125 mg orally QID. Administration of the study drug was for 10 days, and patients were then followed for an additional 4 weeks post-therapy for assessment of relapse.

For this analysis, the modified Intent to Treat (mITT) group of the pooled study population (both FDX and VAN therapies) was used. The mITT population for CC and GC consisted of all patients enrolled into the study who had toxin-positive diarrhea and who received at least one dose of study drug (n=596); the mITT population eligible for assessment of REL additionally required that the patients were a clinical cure (n=518).

Study Inclusion Criteria:
1) >16 years old with a diagnosis of CDI
2) Presence of diarrhea (change in bowel habits with >3 unformed bowel movements in the 24 hours prior to randomization) and positive stool C. difficile toxin A, B, or both within 48 hours of randomization
3) <4 doses (but no more than 24 hours) of vancomycin or metronidazole prior to randomization
4) No doses of other potentially effective treatments for CDI

Study Exclusion Criteria:
1) Life-threatening or fulminant CDI (WBC > 30,000/mm^3, temperature >40°C, or evidence of hypotension and septic shock
2) History of ulcerative colitis or Crohn's disease
3) >1 occurrences of CDI within 3 months of study start
4) Expected use of concomitant antibiotic therapy of more than 7 days

The following independent variables were assessed in a univariate model, with the dependant variable being CC or REL or GC:
- **age** (categorical variable, by decade: 6 categories)
- **albumin** (categorical variable; 3 categories: ≤25, 26-35, or >35)
- **WBC** (categorical variable; 3 categories: <15, 15-25, or >25)
- **Temperature** (categorical variable; 3 categories: <38°C, 38-39°C, >39°C)
- **WBC/Temperature combination** (categorical variable: 3 categories)
- **Infecting Strain type** (dichotomous variable: NAP1/BI or non-NAP1/BI)
- **Concomitant antibiotics** (dichotomous variable: yes or no)

Statistical analyses were done using Fischer's Exact Test.

[The effect of concomitant antibiotics on CC, REL and GC are the subject of another poster presentation at IDSA 2009].

Results

The number of patients in the pooled analysis (both FDX and VAN groups together) for each of the independent variables is shown in table 1.

Table 1. Number of evaluable patients (pooled mITT study population) in each of the independent variable categories

Patient variable	*# patients (%): pooled mITT group for CC and GC*	*# patients (%): pooled mITT group for REL*
Age		
≤ 40	79 (13)	76 (15)
41-50	75 (13)	63 (12)
51-60	110 (18)	96 (19)
61-70	118 (20)	106 (20)
71-80	127 (21)	107 (20)
≥ 81	87 (15)	70 (14)
Albumin		
< 25	159 (27)	122 (24)
26-35	246 (41)	217 (42)
> 35	157 (26)	152 (29)
Missing value	34 (6)	27 (5)
WBC/T° combination		
WBC <15K and T° <38C	421 (71)	376 (73)
WBC 15-25K or T° 38-39C	86 (14)	68 (13)
WBC >25K or T° >39C	17 (3)	12 (2)
Missing both values	72 (12)	62 (12)
Strain type		
NAP1/BI/027	158 (27)	126 (24)
Other	257 (43)	238 (46)
Missing typing	181 (30)	154 (30)

The effect of each of the above variables on CC, REL and GC is shown in table 2.

Table 2. Effect of selected independent variables on clinical cure (CC), relapse (REL), and global cure (GC = CC + no REL)

Patient variable	*CC rate (%)*	*REL rate (%)*	*GC rate (%)*
Age			
P value (among 6 categories)	**0.04**	**0.07**	**0.007**
≤ 40	96.2	14.5	82.3
41-50	84.0	15.9	70.7
51-60	87.3	15.6	73.6
61-70	89.8	24.5	67.8
71-80	84.3	20.6	66.9
≥ 81	80.5	31.4	55.2
Albumin			
P value (among 3 categories)	**< 0.001**	**0.09**	**< 0.001**
≤ 25	76.7	26.2	56.6
26-35	88.2	18.0	72.4
> 35	96.8	16.4	80.9
WBC/T° combination			
P value (among 3 categories)	**0.004**	**0.4**	**0.04**
WBC <15K and T° <38C	89.3	18.6	72.7
WBC 15-25K or T° 38-39C	79.1	17.6	65.1
WBC >25K or T° >39C	70.6	33.3	47.1
Strain type			
P value (among 2 categories)	**< 0.0001**	**0.05**	**0.001**
NAP1/BI/027	79.7	23.8	60.8
Other	92.6	19.3	74.7

Conclusions

In the Phase 3 FDX vs. VAN trial for the therapy of CDI, higher patient age, lower albumin levels, and NAP1/BI/027 infecting strain type were highly correlated with poor outcomes for all 3 endpoints of CC, REL and GC. Patients with higher WBC and fever were less likely to be cured at end of therapy, but this variable did not seem to correlate with CDI relapse.

These data have allowed a qualitative and quantitative evaluation of the relative roles of patient age, albumin, WBC, fever, and strain type on the clinical outcome of CDI in terms of CC, REL, and GC.

Discussion

This large database of CDI patients allowed an in-depth analysis of the role of several factors on the outcome of this infection. Specifically, the CC, REL and GC rates were examined. There were too few patients with serious morbidity (ICU admission or colectomy) and CDI-related mortality to examine these disease outcomes in this study group. However, the analyses showed striking effects of age, albumin, strain type, and WBC/fever on the endpoints measured.

Although "age" has previously been shown to be a significant risk factor for development of CDI and CDI-related mortality,[4,5] this analysis also shows the correlation between age and both CC and REL rates.

Although the extent of WBC/fever predicted CC and GC, it was not correlated with REL.

However, the small number of patients in the group with the highest WBC or fever (n=17) may have limited our ability to detect a trend.

The NAP1/BI/027 strain has also been previously shown to correlate with CDI-related morbidity and mortality,[5] but this analysis also demonstrates its correlation with decreased CC and increased REL rates.

This large database can now be used to create a scoring system based on these easily-obtainable "bedside" variables in order to categorize patients and predict their response to therapy and the probability of relapse. Such a scoring system, if validated, could also be used to select high-risk CDI patients in order to evaluate future therapeutic interventions for their ability to improve patient outcomes.

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