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Geriatric Journal Club  
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"Fidaxomicin versus Vancomycin for Clostridium difficile Infection"  
Thomos J. Louie, MD et al., New England Journal of Medicine 2011;364:422-31

**Background**
- Clostridium difficile colitis (Cdiff) usually develops after broad spectrum antibiotic exposure
- compared to 1990s more cases of decreased clinical response and increased recurrence rates with both metronidazole and vancomycin (20-30%)
- increasing incidence, severity and death in previously low risk population (young, healthy, community dwelling, peripartum)
- due to emergence of hypervirulent strain NAP1/B1/027
- Currently Infectious Disease Society of America treatment guidelines- mild-moderate disease (metronidazole), severe disease (vancomycin) but only vancomycin is FDA approved for Cdiff colitis
- Fidaxomicin is a macrolide antibiotic recently approved by FDA for Cdiff colitis treatment in 18 years or older
- It is hydrolyzed to an active metabolite OP-1118 in GIT, minimally systemically absorbed, has high fecal concentrations (as majority prodrug and active drug excreted in feces), limited activity against normal gut flora, thus overall high active and more selective treatment against Cdiff. It is 8 times more active in vitro than vancomycin even against NAP1/B1/027 strain

**Goal/Hypothesis**
- Compare efficacy and safety of fidaxomicin to vancomycin in treatment of C.diff infection
- Fidaxomicin is non-inferior to vancomycin for the treatment of C.diff

**Methods**
- Phase 3 non-inferiority clinical trial, prospective, multicentre, double-blind, randomized, parallel group trial from May 9, 2006-August 21, 2008. patients recruited from 52 US sites, 15 Canadian sites
- Eligibility criteria: >/= 16 y/o, Diagnosed with Cdiff (diarrhea = change in bowel habits >3 unformed BM /24h period before randomization, AND +Cdiff toxin A/B/both in stool within 48h before randomization), Could have received MAX 4 doses flagyl or vancomycin in 24h period before randomization, did NOT receive any other potentially effective concurrent tx for Cdiff (po bacitracin, fusidic acid, rifaximin)
- Exclusion criteria: Patients with life threatening or fulminant Cdiff infection, toxic megacolon, past exposure to fidaxomicin, ulcerative colitis/crohn's, >1 occurrence Cdiff infection w/in 3 months before start study
- Stratified based on whether current Cdiff infxn FIRST EPISODE (primary occurrence) vs. SECOND EPISODE (first recurrence) w/in 3mths before start of study, then each assigned randomization number and given study medication daily PO q6h x 10d
- assessed daily during 10d course of therapy for clinical cure or failure; which involved following patient for recurrence q wkly x 28d after last dose study med. If developed diarrhea patient would notify study team and be reassessed immediately
- Those that stayed in study and were reassessed between day 36-40 were randomized again and reassessed for recurrence
- clinical cure = resolved diarrhea = <= 3 unformed stools x 2 consecutive days PLUS maintenance of resolution for duration therapy AND no further need for Cdiff treatment by 2nd day after end of treatment course (subjective by investigator's opinion)
- clinical failure = persistent diarrhea and/or need for more Cdiff treatment (in opinion of investigator)
• global cure = resolved diarrhea w/o recurrence
• clinical recurrence = reappear >3 diarrhea stools per 24h period w/in 4 weeks after completing therapy, (+) Cdiff toxin A/B/both in stool, need for retreatment for Cdiff
• main outcome measures: primary efficacy end point (rate of clinical cure in 'modified intention-to-treat' (MIT) and 'per-protocol' populations at end of therapy or at time of early withdrawal from study), 2 secondary efficacy end points (recurrence of Cdiff infection during 4 week period after completing therapy and global cure in MIT and 'per protocol' population)
• at set points in trial stool samples collected for Cdiff toxin assay, blood and fecal samples for fidaxomicin levels
• safety continually assessed from day informed consent to last dose study (via physical exam, EKG, cbc w/ diff, chem 13, UA); patient able report adverse events

Statistical Analysis
• noninferiority study with set one-sided lower 97.5% CI to analyze primary end point. with noninferiority margin of -10%, lower boundary confidence limit within 10% point margin demonstrates clinical noninferiority
• secondary end points (recurrence, overall cure) analyzed by post-hoc analysis using 2 sided test of population proportions based on normal approximation to binomial distribution at significance level 0.05

Results
• Figure 1 -randomization and follow up -629 enrolled and randomize d-->302 (fidaxomicin), 327 (vancomycin) -->after meeting inclusion criteria/withdrawals-->548 could be evaluated for per-protocol analysis
• Similar adherence both groups in MIT and per protocol groups in both vancomycin and fidaxomicin groups
• Table 1. baseline characteristics without significant difference
• Figure 2. primary end point clinical cure met criterion for noninferiority in both MIT (88.2% fidaxomicin, 85.8% vancomycin group; lower boundary 97.5% CI for difference -3.1) and 'per-protocol' populations (92.1%, 89.8% respectively; lower boundary 97.5%CI of -2.6% points) populations within lower boundary 97.5% CI for difference in cure rates of -3.1
• fidaxomicin significantly lower rate recurrence than vancomycin in both MIT (15.4% vs. 25.3%; decrease 9.9% points with fidaxomicin; 95% CI -16.6 to -2.9; p = 0.005) and per-protocol population (13.3% vs. 24%; decrease 10.7%points with fidaxomicin; 95% CI, -17.9 to -3.3; p = 0.004)

Discussion
• Pros:
  • Fidaxomicin BID PO vs. QID vancomycin
  • Bacteriocidal vs. bacteriostatic --> Prolong postantibx effect may prevent relapse over longer period
  • No plasma accumulation
  • maintains normal gut flora “colonization resistance”
  • Prevents intro or persistence of pathogens and may inhibit reemergence Cdiff
  • Theoretically decreases selection for overgrowth of vanc-resistant enterococci
  • Vancomycin sparing effect- decr rate of VRE
  • Overall similar effectiveness wrt clinical resolution acute diarrhea 2/2 Cdiff but more sustained/durable resolution dz (improved global cure) with fidaxomicin
• Cons:
  - Funded by Optimer Pharmaceuticals who manufactures drug
  - 1st version of paper written by part-time employee of Optimer Pharmaceuticals
• Data presentation and writing style highly biased
  • Relative Risk reduction calculated rather than Attributable Relative Risk

Limitations
• excluded severely ill eg. toxic megacolon
• ?ability to involve sicker patients in next study as not shown to have statistically significant difference in clinical cure rate compared to vancomycin in either modified intention-to-treat or per-protocol populations
• very expensive, 1 tab = $168, therapy course $3360

Application
• Problematic issue with Cdiff infection is rate of recurrence and its associated morbidity, mortality. Fidaxomicin is noninferior to vancomycin in rate of clinical cure, has moderate absolute reduction of recurrence but it is drastically more expensive (1 tab = $168, therapy course $3360) and no IDSA guidelines as when to implement Fidaxomicin. To consider use individual severe or recurrent disease with vancomycin allergy