Fidaxomicin vs Vancomycin for Clostridium difficile Infection

GERIATRIC GRAND ROUNDS
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Overview

- Since 1990s > 2x↑ incidence Cdiff infection
- ~3 million cases/yr in US
  - most common bacterial cause of diarrhea in US
- ↑ incidence, severity, mortality and infection in prior low risk population (young, healthy, community-dwelling, peripartum)
- ↓ clinical response to vancomycin/flagyl with ↑ relapse rates
new hypervirulent strain NAP1/BI/027
- Emergence strongly correlates with fluoroquinolones
- Produces more exotoxin A/B and additional binary toxin \( \rightarrow \) more serious, refractory infection with ↑ rates toxic megacolon requiring colectomy

But not all treatment failure and relapse due to BI-strain
BI/NAP1 Strain C. diff

Figure 2. States with the North American Pulsed Field Type 1 (BI/NAP1) strain of C. difficile confirmed by CDC as of November 15, 2005 (N=16).
• Increasing nosocomial incidence + severity especially if >65 y/o
  ○ 20-50% adult carriers in hospitals and long term care facilities
  ○ 20% patients with stool culture negative on admission become infected during hospitalization

• Especially severe infxn if
  ○ Comorbidities eg. Advanced age
  ○ Disturbed gut normal flora (eg. Antibiotics, antitumor meds)
Clostridium difficile

- 4 clinical forms
  - Short-term colonization - usually develop in health care facility
  - Acute diarrhea - mild-severe
  - Fulminant diarrhea +/- pseudomembranous colitis
  - Toxic megacolon
### Treatment Guidelines

### Infectious Disease Society of America (IDSA)

- **Mild-mod:** Metronidazole IV/PO
- **Severe:** Vancomycin PO

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DOSAGE REGIMEN</th>
<th>COST PER DOSE</th>
<th>COST PER TX COURSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>500mg po TID x 10-14d</td>
<td>$0.73</td>
<td>$21.90 (10d), $30.66 (14d)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>125mg po QID x 10-14d</td>
<td>$31.83</td>
<td>$1273 (10d), $1782 (14d)</td>
</tr>
</tbody>
</table>
## Treatment

<table>
<thead>
<tr>
<th>Metronidazole</th>
<th>Vancomycin</th>
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</table>
| - biliary excreted $\rightarrow$ fecal concentration but large amount absorbed by gut $\rightarrow$ low drug levels at mucosal/intraluminal level  
  - Thus, **high failure rate**  
- Complications-dose-dep peripheral neuropathy, nausea, metallic taste  
- NOT FDA-approved for treatment C.diff infections | - Poor GIT absorption $\rightarrow$ max concentration intracolonically  
- Complications- systemic absorption $\rightarrow$ Renal tox |
Treatment failure

- After successful initial treatment with flagyl or vancomycin 20-30% recurrent Cdiff w/in 60days (usually 1st 2 weeks)
- Retreatment with either med resolves infection in most patients but 1/3 have >/=1 more recurrence, increases morbidity/mortality
- Risk factors for recurrence
  - >65 y/o, severe underlying comorbidities (immunosuppression, increase risk of requiring antibiotics/hospitalization), gastric acid suppression, need for ongoing antibiotics during treatment for cdiff
Treatment Failure/Recurrence

- Increased frequency of recurrent disease in hospitalized and outpatients creates pathogen reservoir leading to secondary infxn in other exposed patients
Fidaxomicin

- Macroclide, hydrolyzed to active metabolite
- Bactericidal; inhibits RNA polymerase
- Narrow spectrum-GP esp Cdiff, most staph, enterococci; no GN/fungi
- No cross-resistance with other antibx
- 8x more active in vitro than vancomycin against Cdiff including NAP1/BI/027 strain
- Minimal systemic absorption
  - High fecal concentration
  - less disruption of gut normal flora
  - Thus, highly active and more selective therapy against Cdiff
  - And possibly less systemic side effects
Study Design

- Prospective, multicenter, double-blind, randomized, parallel group trial
- May 6, 2006 - August 21, 2008
- Phase 3 noninferiority study comparing efficacy and safety of fidaxomicin with vancomycin in treatment of Cdiff infection
Study Population

- 52 US sites, 15 Canadian sites
- Eligibility criteria:
  - \( \geq 16 \) y/o
  - Diagnosed with Cdiff
    - Diarrhea = change in bowel habits \( \geq 3 \) 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
  - NOT on potentially effective concurrent treatment for Cdiff (eg. Bacitracin PO, fusidic acid, rifaximin)
Exclusion Criteria

- life threatening or fulminant Cdiff infxn
  - Wbc>30k, T>104F, sbp<90, septic shock, peritoneal signs, significant dehydration
- Toxic megacolon
- Past exposure to fidaxomicin
- Pregnancy or breastfeeding
- Ulcerative colitis/crohn’s
- >1 occurrence Cdiff w/in 3mths before start of study
- Likelihood of death w/in 72h from any cause
Randomization and Treatment

- Stratified based on whether current Cdiff FIRST EPISODE (primary occurrence) vs. SECOND EPISODE (first recurrence) w/in 3mths before start of study
- Computer generated randomization # and medication kit # assigned to each patient
- Assessed qd for clinical cure vs. failure x 10d therapy
- Patients given study medication daily PO q6h x 10 d
  - Fidaxomicin 200mg PO q12h with intervening placebo, OR
  - Vancomycin 125mg PO q6h
- If met criteria clinical cure → assessed for recurrence q wk x 28d after last dose study med → if (+) diarrhea, to notify study team → reassess immediately
### Definitions

#### Clinical cure
- Resolution diarrhea ($\leq 3$ unformed stools /2 consecutive days)
- Maintain resolution w/o need restart Cdiff therapy by 2$^{nd}$ day after complete course therapy (investigator’s opinion)
- Marked ↓$\#$ unformed stool at end therapy but residual mild ab discomf w/o need more Cdiff therapy (investigator’s opinion)

#### Clinical failure
- Persistent diarrhea
- Need for more Cdiff therapy
- Investigator’s opinion
### Definitions

- **Global cure**
  - Resolution diarrhea w/o recurrence

- **Patients who stayed in study, had follow up assessment D36-D40 after randomization were assessed for recurrence**

- **Clinical recurrence**
  - >3 diarrheal stools/24h within 4 weeks after completing therapy
  - (+) stool Cdiff toxin A/B/both
  - Needed retreatment Cdiff
629 Patients were enrolled and underwent randomization

327 Were assigned to receive vancomycin
- 4 withdrew before treatment
- 6 had ≤3 bowel motions in 24 hr
- 8 tested negative for *C. difficile* toxin

309 (94.5%) Were included in modified intention-to-treat analysis
- 14 had <3 days treatment in the case of failure
- 7 had <8 days treatment in the case of cure
- 1 had no end-of-therapy evaluation
- 2 had concomitant therapy for *C. difficile* infection
- 2 had other protocol violation

283 (86.5%) Were included in the per-protocol analysis
- 15 had <25 days follow-up and no recurrence, or >30 days follow-up with recurrence
- 11 had concomitant therapy for *C. difficile* infection
- 1 had other protocol violation

221 had clinical cure and could be evaluated for recurrence

302 Were assigned to receive fidaxomicin
- 2 withdrew before treatment
- 4 had ≤3 bowel motions in 24 hr
- 9 tested negative for *C. difficile* toxin

287 (95.0%) Were included in modified intention-to-treat analysis
- 12 had <3 days treatment in the case of failure
- 5 had <8 days treatment in the case of cure
- 1 had no end-of-therapy evaluation
- 2 had concomitant therapy for *C. difficile* infection
- 2 had other protocol violation

265 (87.7%) Were included in the per-protocol analysis
- 12 had <25 days follow-up and no recurrence, or >30 days follow-up with recurrence
- 12 had concomitant therapy for *C. difficile* infection
- 9 had other protocol violation
- 21 had clinical failure

211 had clinical cure and could be evaluated for recurrence
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Modified Intention-to-Treat Population</th>
<th>Per-Protocol Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fidaxomicin (N = 287)</td>
<td>Vancomycin (N = 309)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60.3±16.9</td>
<td>62.9±16.9</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>57.1</td>
<td>54.7</td>
</tr>
<tr>
<td>Unformed stools per day (no.)</td>
<td>8.1±4.2</td>
<td>8.3±5.4</td>
</tr>
<tr>
<td>Inpatient (%)</td>
<td>58.2</td>
<td>60.5</td>
</tr>
<tr>
<td>Lack of response to metronidazole (%)</td>
<td>4.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Treatment for C. difficile infection in previous 24 hr (%)</td>
<td>38.3</td>
<td>39.8</td>
</tr>
<tr>
<td>Previous episode of C. difficile infection (%)</td>
<td>16.7</td>
<td>17.5</td>
</tr>
<tr>
<td>BI/NAP1/027 strain (%)†</td>
<td>37.5</td>
<td>38.6</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant between-group differences.
† Percentages are based on the 415 patients who had a strain type that could be evaluated.
Outcomes

- **Primary efficacy end point**
  - Rate clinical cure in Modified-intention-to-treat (mITT) + Per-protocol (PP) population at end therapy or at time early withdrawal from study
  - With documented adherence to protocol and had end-of-therapy evaluation

- **Secondary efficacy end point**
  - Recurrence Cdiff w/in 4 weeks after end therapy
  - Global cure in mITT + PP
Safety

- Assessed from day informed consent – last dose study drug given or last study visit (whichever came later)
- Physical exam, EKG, CBC, BMP, UA
- Adverse events reported, if > once per patient counted only as single incidence for particular adverse event
- Common adverse events: nausea, vomiting, ab pain, anemia, neutropenia. But no subject withdrew due to intolerance or allergy to study medication
Results

- Noninferiority study used one-sided lower 97.5% CI to analyze primary end point, with noninferiority margin of -10% points.

- **Primary end point** of clinical cure in both mITT + PP met noninferiority criterion. In mITT: 88.2% fidaxomicin group, 85% vancomycin group (lower boundary of 97.5% CI for difference cure rates -3.1% points), PP: 92.1% fidaxomicin group, 89.8% vancomycin group (lower boundary of 97.5% CI of -2.6% points).
Clinical Outcome
Rates of Primary and Secondary Endpoints

- **Clinical Cure**
  - mITT: 88.2% Fidaxomicin, 85.8% Vancomycin, P=0.005
  - PP: 92.1% Fidaxomicin, 89.8% Vancomycin

- **Recurrence**
  - mITT: 15.4% Fidaxomicin, 25.3% Vancomycin, P=0.004
  - PP: 13.3% Fidaxomicin, 24.0% Vancomycin

- **Global Cure**
  - mITT: P=0.006
  - PP: 77.7% Fidaxomicin, 67.1% Vancomycin, P=0.006
Results

- **Secondary end point** analysis - Fidaxomicin associated with significantly lower rate of recurrence than vancomycin in both mITT (15.4% vs. 25.3%; a reduction with fidaxomicin of 9.9% points; 95%CI, -16.6 to -2.9, p =0.005) and PP (13.3% vs. 24.0%; a reduction with fidaxomicin of 10.7% points; 95%CI, -17 to -3.3; p=0.004)
### Clinical Outcome

**Table 3. Rates of Recurrence of *C. difficile* Infection, According to Subgroups, in the Modified Intention-to-Treat and Per-Protocol Populations.**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Modified Intention-to-Treat Population</th>
<th>Per-Protocol Population</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Fidaxomicin no./total no. (%)</td>
<td>Vancomycin no./total no. (%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>19/150 (12.7)</td>
<td>27/134 (20.1)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>20/103 (19.4)</td>
<td>40/131 (30.5)</td>
</tr>
<tr>
<td>Hospital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>24/136 (17.6)</td>
<td>40/146 (27.4)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>15/117 (12.8)</td>
<td>27/119 (22.7)</td>
</tr>
<tr>
<td>Previous episode of <em>C. difficile</em> infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30/211 (14.2)</td>
<td>52/217 (24.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>9/42 (21.4)</td>
<td>15/48 (31.2)</td>
</tr>
<tr>
<td>Treatment for current episode of <em>C. difficile</em> infection in previous 24 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16/88 (18.2)</td>
<td>25/97 (25.8)</td>
</tr>
<tr>
<td>No</td>
<td>23/165 (13.9)</td>
<td>42/168 (25.0)</td>
</tr>
<tr>
<td>Severity of disease at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>7/59 (11.9)</td>
<td>20/68 (29.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>20/102 (19.6)</td>
<td>18/88 (20.5)</td>
</tr>
<tr>
<td>Severe</td>
<td>12/92 (13.0)</td>
<td>29/109 (26.6)</td>
</tr>
<tr>
<td>Strain type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAP1/BI/027</td>
<td>16/59 (27.1)</td>
<td>14/67 (20.9)</td>
</tr>
<tr>
<td>Non–NAP1/BI/027</td>
<td>12/117 (10.3)</td>
<td>34/121 (28.1)</td>
</tr>
<tr>
<td>Concomitant systemic antimicrobial therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14/81 (17.3)</td>
<td>25/90 (27.8)</td>
</tr>
<tr>
<td>No</td>
<td>25/172 (14.5)</td>
<td>42/175 (24.0)</td>
</tr>
</tbody>
</table>
Results

- In PP population BI-strain: similar rates recurrence in fidaxomicin 24.4%, vancomycin 23.6% (p=0.93)

- In PP population Non-BI strains: lower rate recurrence fidaxomicin 7.8% vs. vancomycin 25.5% (reduction with fidaxomicin of 17.7% points; 95%CI, -27.5 to -7.9; p<0.001)
Safety

- No significant difference rate adverse events or serious adverse events between fidaxomicin and vancomycin groups
- Occurrence any adverse event 62.3% fidaxomicin, 60.4% vancomycin; serious adverse event 25.0%
Conclusion

- This phase 3 randomized clinical trial found the rate of clinical cure of Cdiff infections with fidaxomicin was noninferior to vancomycin.

- Fidaxomicin was associated with significantly lower rate of recurrence of Cdiff infection with non-NAP1/BI/027 strain within 4 weeks after conclusion of treatment.
Discussion

- **Pros**
  - Fidaxomicin BID PO vs. QID vancomycin
  - Bacteriocidal vs. bacteriostatic
    - Prolong postantibx effect may prevent relapse over longer period
  - No plasma accumulation
  - Does not kill gut NF maintaining “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- dect 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
Discussion

• 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
  ○ Excluded severely ill-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
  ○ $$$
Discussion

- Concern for oral flagyl or vancomycin induced vancomycin-resistant enterococci
- 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 in individuals with severe or recurrent disease with vancomycin allergy
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