Formulary & positioning of fidaxomicin

Professor Mark Wilcox

Leeds Teaching Hospitals,
University of Leeds,
Public Health England
Potential Conflicts of Interest

I have received:

- Consulting fees from Actelion, Astellas, Astra-Zeneca, Cerexa, Durata, Cubist, Merck, Nabriva, Novacta, Novartis, Optimer, Pfizer, Roche, Sanofi-Pasteur, Summit, The Medicines Company and VH Squared;

- Lecture fees from Pfizer, Astra-Zeneca and Astellas;

- Grant support from Actelion, Astellas, bioMerieux, Cerexa, Cubist, Merck, Roche, Sanofi-Pasteur, Summit, The Medicines Company.
“In politics,

when you are in doubt what to do, do nothing ...
when you are in doubt what to say, say what you really think.”

Winston Churchill
1905
Q Should fidaxomicin be on the formulary?
A Yes

Q What is the correct positioning of fidaxomicin?
A For all recurrences (assuming not rcvd previously), and for serious CDI cases with high risk of recurrence


Fidaxomicin - the facts (i)

- Two, phase 3, multi-centred, randomised, double-blind trials had almost identical designs and compared oral fidaxomicin (dose: 200 mg bd for 10–14 days) with oral vancomycin (dose: 125 mg qds for 10–14 days). The studies had essentially similar results.

- Fidaxomicin was non-inferior to vancomycin in the initial clinical cure of CDI (relative risk (RR) 0.88 (95% CI 0.64, 1.19), p=0.396), but was superior in reducing recurrence (RR 0.54 (95% CI 0.42, 0.71), p<0.001) and sustained clinical cure (RR 0.68 (95% CI 0.56, 0.81), p<0.001) (all modified intention to treat analysis of combined study results).

Louie et al., 2011; Cornely et al., 2012; Crook et al., 2012.
Fidaxomicin phase 3 trials - time to recurrence

Early recurrence:
Fidaxomicin: 7.4%
Vancomycin: 19.3%
p<0.001

Late recurrence:
Fidaxomicin: 7.3%
Vancomycin: 8.4%
p=0.560

Day of follow-up after completion of therapy for CDI

Fidaxomicin - the facts (ii)

- The side-effect profile of fidaxomicin appears similar to that of oral vancomycin (some reports of hypersensitivity rashes*).

- The acquisition cost of fidaxomicin is considerably higher than vancomycin (which is more expensive than metronidazole).

- Oral fidaxomicin was approved for the treatment of CDI in Europe in 2012, and has been reviewed by NICE (the information published by NICE is not formal guidance) and the Scottish Medicines Consortium (SMC).

Louie et al., 2011; Cornely et al., 2012; Crook et al., 2012; Iarikov et al., CID 2103*.
Fidaxomicin - the facts (iii)

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Fidaxomicin - SMC, NICE

- SMC concluded that fidaxomicin is appropriate for the treatment of adults with a first episode of CDI recurrence, on the advice of local microbiologists or specialists in infectious diseases (SMC, 2012).

- NICE concluded that fidaxomicin may have advantages in reducing the rate of recurrence, and that local decision makers should take into account the potential benefits alongside the medical need, the risks of treatment, and the relatively high cost of the antibiotic in comparison with other CDI treatment options.

- NICE summary does not represent formal NICE guidance.

http://publications.nice.org.uk/clostridium-difficile-infection-fidaxomicin-esnm1/
Only limited cost effectiveness data on the use of fidaxomicin in CDI have been published.

SMC accepted that there was an economic case to justify the use of fidaxomicin in patients with first CDI recurrence.

For the population of patients with severe CDI, however, a convincing economic case for fidaxomicin was not demonstrated.

Assuming a number-needed-to-treat for sustained clinical response = 7.1 patients, fidaxomicin represented value for money from the perspective of the US health system.
Fidaxomicin - cost-effectiveness (ii)

- “Given the current cost and NAP1/BI/027 accounting for ~50% of isolates, using fidaxomicin as a first-line treatment for CDI is not cost-effective.”
- “However, typing and treatment with fidaxomicin based on strain may be more promising depending on the costs of FDX.”
- However,
  - No accounting for effect of financial penalties
  - CD027 rate <10% in UK (and falling)
  - No attempt to cost deaths
  - Authors assumed that metronidazole was equally effective against 027 vs non-027 cases

Fidaxomicin

- Less effective against CD 027 (but same true for vancomycin)
- Some resistance emergence in VRE (not in CD)
- CLOSER study, ~1000 isolates across Europe, no resistance
- No fidaxomicin resistance in CD, but one isolate (cure patient) MIC = 16 mg/L
- Effect of concomitant antibiotics
Determinants of recurrence risk

- Flora inhibition (antibiotics)
- Spore persistence
- Antibody deficit
- Previous recurrence
- Strain type
- Host biomarkers e.g. albumin
- Age
- Co-morbidities
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Effect of CA on outcome after treatment of CDI with fidaxomicin or vancomycin

<table>
<thead>
<tr>
<th></th>
<th>No CA</th>
<th>CA</th>
<th>p value</th>
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</thead>
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<tr>
<td><strong>Clinical cure (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>CA during treatment*</td>
<td>93%</td>
<td>84%</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Recurrence (%)</strong></td>
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<tr>
<td>CA during treatment*</td>
<td>18%</td>
<td>24%</td>
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<tr>
<td>CA during follow-up†</td>
<td>18%</td>
<td>25%</td>
<td>0.06</td>
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<tr>
<td>CA at any time‡</td>
<td>18%</td>
<td>23%</td>
<td>0.08</td>
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<tr>
<td><strong>Sustained response (%)</strong></td>
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<tr>
<td>CA at any time‡</td>
<td>75%</td>
<td>66%</td>
<td>0.005</td>
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<tr>
<td><strong>Median time to resolution of diarrhoea (h)</strong></td>
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<tr>
<td>CA during treatment*</td>
<td>54</td>
<td>97</td>
<td>&lt;0.001</td>
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Algorithm 1. 1st episode of *Clostridium difficile* infection (CDI)

Diarrhoea **AND** one of the following:
- Positive *C. difficile* toxin test **OR** Results of *C. difficile* toxin test pending **AND** clinical suspicion of CDI

If clinically appropriate discontinue non-*C. difficile* antibiotics to allow normal intestinal flora to be re-established
- Suspected cases must be isolated

**Symptoms/signs: not severe CDI**
- (None of: WCC >15, acute rising creatinine and/or colitis)
- Oral metronidazole 400mg 8-hourly 10-14 days

**Daily Assessment**

**Symptoms improving**
- Diarrhoea should resolve in 1-2 weeks
- Recurrence occurs in ~20% after 1st episode; 50-

**Symptoms/signs: severe CDI**
- WCC >15, acute rising creatinine and/or colitis
- Oral vancomycin 125 mg 6-hourly 10-14 days.
- Consider oral fidaxomicin 200 mg 12-hourly 10-14 days in patients with multiple co-morbidities who are receiving concomitant antibiotics

**Daily Assessment**

**Symptoms not improving or worsening**
- Should not normally be deemed a treatment failure until day 7 of treatment.
Algorithm 2 Recurrent *Clostridium difficile* infection (CDI)

Recurrence of diarrhoea (at least 3 consecutive type 5-7 stools) within ~30 days of a previous CDI episode AND positive *C. difficile* toxin test

Must discontinue non-*C. difficile* antibiotics if at all possible to allow normal intestinal flora to be re-established
- Review all drugs with gastrointestinal activity or side effects
  - (stop PPIs unless required acutely)
  - Suspected cases must be isolated

**Symptoms/signs: not life-threatening CDI**
- Oral fidaxomicin 200 mg 12-hourly for 10-14 days
  - (efficacy of fidaxomicin in patients with multiple recurrences is unclear)
  - Depending on local cost-effectiveness decision making,
    - Oral vancomycin 125 mg 6-hourly 10-14 days is an alternative

**Daily Assessment**
- (include review of severity markers, fluid/electrolytes)
Summary

- Fidaxomicin confers reduced risk of recurrence in comparison with established treatment options for CDI
- It has a high acquisition cost
- Economic analyses are contradictory and only tell us so much
- Would you want metronidazole, vancomycin or fidaxomicin to treat your CDI?