CA-ADAP Drug Review: Fidaxomicin (DIFICID) for Clostridioides difficile

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CA-ADAP Drug Review: AGENDA

1. Drug Background and Information
2. Disease Background
3. Clinical Trials
4. Discussion
Fidaxomicin (DIFICID)

• **Indication:** For treatment of *C. difficile*-associated diarrhea in adult and pediatric patients 6 months+

• **Dosage and Administration:**
  - Adults: One (1) 200mg tablet by mouth twice daily x10days
  - Pediatrics (6 mos - <18yrs):
    - Tablets – weight at least 12.5kg: One (1) 200mg tablet by mouth twice daily x10days
    - Oral Suspension – weight at least 4kg: Weight-based dosing of oral suspension (included in package insert)
Fidaxomicin Safety Information

• Acute hypersensitivity reactions have been reported
• The most common adverse reactions in adults:
  − Nausea (11%)  - GI Hemorrhage (4%)
  − Vomiting (7%)  - Anemia (2%)
  − Abdominal pain (6%)  - Neutropenia (2%)
• The most common adverse reactions in pediatric patients:
  − Pyrexia (13.3%)  - Diarrhea (7.1%)
  − Abdominal pain (8.2%)  - Constipation (5.1%)
  − Vomiting (7.1%)  - Increased aminotransferases/rash (5.1%)
Bacterial Enteric Infections & PLWH

- Rates of Gram-negative infections are at least 10x higher
  - Rates decline when treated with ART
- *C. diff*-associated infection (CDI) is common
  - Low CD4 count (<50 cells/mm$^3$) is a disease risk factor
- Incidence of community-onset CDI is increasing
  - Health care providers should consider CDI when evaluating outpatient diarrheal illnesses
- The likely source for infections is contaminated food/water
  - Sexual activity with fecal-oral exposure increases risk
  - HIV-associated alterations in mucosal immunity or intestinal integrity, + treatment with acid-suppressants may increase risk
- Severe infection often is defined as six (6) or more loose stools/day
  - The risk of more serious illness increases with immunosuppression
C. Difficile diarrhea

- Patients at risk for *C. diff* diarrhea include:
  - Received/currently receiving antibiotics (including prophylaxis)
  - Hospitalization in past 4-6 weeks
  - Reside in LTC
  - CD4<200 cells/mm$^3$
  - Taking acid-suppressive meds
- Only those with diarrhea (3+ loose stool/24hr) should be tested for *C. diff*
- Only stool samples that take the shape of the container should be tested for *C. diff* toxin B.
CDI Treatment

• Initial Episode:
  - Fidaxomicin increased the likelihood of sustained clinical response compared to oral vancomycin (RR 1.16; 95% CI, 1.09-1.24)
  - Fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events, and all-cause mortality
  - The 2021 IDSA CDI guidelines update for adults suggests treatment with fidaxomicin, rather than oral vancomycin, for initial CDI, whether CDI is severe or nonsevere
    - Fidaxomicin should be considered in PLWH and CDI
      • Oral vancomycin is still also acceptable
      • Metronidazole is considered an alternative to fidaxomicin and vancomycin
Clinical Trials
Efficacy and safety of fidaxomicin for the treatment of *Clostridioides difficile* infection

- **Objective:** To demonstrate non-inferior efficacy of fidaxomicin vs vancomycin

- Phase III, vancomycin-controlled, double-blind, parallel group study
  - 212 patients randomly assigned fidaxomicin 200mg BID or vancomycin 125mg QID x 10 days
  - Primary endpoint was global cure rate of CDI

- **Results:**
  - Non-inferiority margin set at 10%
    - Fidaxomicin: 70/104 (67.3%) cured
    - Vancomycin: 71/108 (65.7%) cured
    - Non-inferiority was not demonstrated
  
  - Post-hoc analysis of patients who received at least 3 days’ treatment
    - Fidaxomicin: 70/97 (72.2%) cured
    - Vancomycin: 71/106 (67.0%) cured
    - Recurrence rate was lower in fidaxomicin (19.5%) than vancomycin (25.3%)
Extended-pulsed fidaxomicin vs vancomycin for *Clostridioides difficile* infection in patients 60 years and older (EXTEND)

• **Objective:** To compare clinical outcomes of extended-pulsed fidaxomicin with standard vancomycin

• Randomized, controlled, open-label, superiority study
  - 364 hospitalized adults aged 60+ with confirmed *C. diff* infection
  - Patients assigned fidaxomicin 200mg BID on days 1-5, then Qday on alternate days 7-25 or vancomycin 125mg QID on days 1-10

• **Results:**
  - Fidaxomicin: 124/177 (70%) cured
  - Vancomycin: 106/179 (59%) cured
  - Incidence of adverse events did not differ between the groups
  - Extended-pulsed fidaxomicin was superior to standard-dose vancomycin
  - Recurrence rates with fidaxomicin were the lowest observed thus far (from date of publishing) for *C. diff* infection
Fidaxomicin versus vancomycin for infection with Clostridium difficile

- **Objective:** To compare efficacy and safety of fidaxomicin with vancomycin
- **Multicenter, double-blind, randomized, non-inferiority trial**
  - 535 patients aged 16+ assigned fidaxomicin 200mg Q12h or vancomycin 125mg Q6h x10 days
  - Primary endpoint was clinical cure

- **Results:**
  - Non-inferiority margin set at 10%
  - Fidaxomicin: 198/216 (91.7%) cured
  - Vancomycin: 213/235 (90.6%) cured
  - Non-inferiority **was** demonstrated (one-sided 97.5% CI -4.3%)
  - Occurrence of ADRs did not differ between groups
  - 20/264 fidaxomicin and 17/260 vancomycin died
Fidaxomicin versus vancomycin for Clostridium difficile infection

- **Objective:** To compare efficacy and safety of fidaxomicin with vancomycin
- **Phase III, randomized, double-blind, parallel group study**
  - 629 patients assigned fidaxomicin 200mg BID or vancomycin 125mg QID x10 days
  - Primary endpoint was clinical cure
  - Secondary endpoints were recurrence of C. diff infection within 4 weeks after treatment and global cure (no recurrence)
- **Results:**
  - Non-inferiority margin set at 10%
    - Fidaxomicin: 92.1% cured
    - Vancomycin: 89.8% cured
    - Non-inferiority was **not** demonstrated
    - Significantly fewer patients in fidaxomicin group had recurrence
    - ADRs similar for both
Treating *Clostridioides difficile*-associated infection (CDI)

**Preferred Therapy (Severe or Nonsevere CDI*)**
- Fidaxomicin 200mg (PO) 2 times per day for 10 days
- Vancomycin 125mg (PO) 4 times per day for 10 days

**Alternative Therapy for Nonsevere CDI***
- If fidaxomicin or vancomycin access is limited and if CDI is nonsevere, outpatient disease: metronidazole 500mg PO 3 times per day for 10 days

**Note:** Based on clinical trials, vancomycin is superior to metronidazole for therapy of CDI
Formulary Management
Recommendations: *C. diff* Treatment

Fidaxomicin (DIFICID)  Recommend addition to the ADAP formulary.
References

1. Merckconnect.com. 2021. DIFICID® (fidaxomicin) | Official Site. [online] Available at: <https://www.merckconnect.com/dificid/coverage/?gclid=EAIaIQobChMI9sywu9bk9wIVig2tBh0YaQL0EAYASAAEgLdFd_BwE&gcslrc=aw.ds> [Accessed 16 May 2022].


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