Antimicrobial Activities of Fidaxomicin

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Fidaxomicin is bactericidal against Clostridium difficile. The combined results of 8 in vitro studies of 1323 C. difficile isolates showed the minimum inhibitory concentration (MIC) range of fidaxomicin to be ≤0.001–1 µg/mL, with a maximum MIC for inhibition of 90% of organisms (MIC₉₀) of 0.5 µg/mL. Isolates from 2 phase III clinical trials demonstrated that fidaxomicin MICs of baseline isolates did not predict clinical cure, failure, or recurrence of C. difficile infections. No resistance to fidaxomicin developed during treatment in either study, although a single strain recovered from a cured patient had an elevated MIC of 16 µg/mL at the time of recurrence. For 135 strains, OP-1118, a major metabolite, had an MIC for inhibition of 50% of organisms of 4 µg/mL and an MIC₉₀ of 8 µg/mL. Changes in inoculum size (10²–10⁵ colony-forming units/spot) or cation concentrations of calcium or magnesium appeared to have no effect on fidaxomicin MICs. Fidaxomicin has little or no activity against gram-negative aerobes and anaerobes or yeast.

In 1991, Swanson et al [1] evaluated the in vitro activity of tiacumicin B (now fidaxomicin) isolated from the fermentation broth of Dactylosporangium aurantiacum subspecies hamdenensis [2] against Clostridium difficile. Fidaxomicin (formerly designated OPT-80 and PAR-101) has been developed for the treatment of C. difficile-associated diarrhea and is a potent new macrocyclic antibiotic that targets RNA polymerase. Fidaxomicin has a narrow spectrum of activity, with little or no activity against gram-negative aerobic and anaerobic bacteria, but demonstrates high activity against C. difficile (Table 1) [3]. Fidaxomicin reaches a high concentration in the gut with minimal systemic absorption. This article reviews and provides original data for the antimicrobial activity of fidaxomicin, including variations of test conditions and activity of its metabolite OPT-1118, as well as its kill kinetics and pharmacodynamics as related to C. difficile.

Comparative In Vitro Studies

Eight studies performed on strains isolated between 1983 and 2010 have reported the comparative in vitro activity of fidaxomicin against C. difficile [1, 4–10] (Table 2). A combined total of 1323 isolates were reported with a minimum inhibitory concentration (MIC) range of ≤0.001–1 µg/mL and a maximum MIC for inhibition of 90% of organisms (MIC₉₀) of 0.5 µg/mL, which are far below the fidaxomicin levels found in feces after treatment.

Hecht et al [6] reported on the in vitro activity of fidaxomicin against 110 toxigenic C. difficile clinical isolates collected during 1983–2004 in the United States, South America, and Europe. With the use of the Clinical and Laboratory Standards Institute (CLSI) [11] supplemented Brucella agar dilution method, the fidaxomicin geometric mean MIC was 0.081 µg/mL, with a maximum MIC of 0.25 µg/mL and an MIC₉₀ of 0.125 µg/mL. They did not note any variation of MIC related to year of isolation or restriction endonuclease analysis (REA) BI group status. A German study [4] that used the Wilkins-Chalgren broth microdilution method on isolates collected between 1986 and 2002 showed that all C. difficile strains were susceptible to ≤0.06 µg/mL of fidaxomicin and confirmed low MICs by agar dilution for a subset of isolates. A Manitoba, Canada, study [8] that used the CLSI agar dilution method on isolates collected between January and

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Clinical Infectious Diseases 2012;55(52):S143–8
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DOI: 10.1093/cid/cis339

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Table 1. Antimicrobial Profile of Fidaxomicin for Various Aerobic and Anaerobic Bacteria and Yeast

| Strain-Negative Bacteria          | ATCC No. | FDX MIC | Gram-Positive Bacteria         | ATCC No. | FDX MIC | Yeast                      |
|----------------------------------|----------|---------|-------------------------------|----------|---------|----------------------------|
| Acinetobacter baumannii          | 19606    | >32     | Bacillus cereus               | 11778    | 1       | Candida albicans            |
| Acinetobacter calcoaceticus      | 23055    | 1       | B. cereus                     | 14579    | 1       | Candida albicans            |
| Bacteroides distasonis           | 8503     | >32     | Clostridium difficile         | 43255    | 0.125   | Candida krusei              |
| Bacteroides fragilis             | 23745    | >32     | C. difficile                  | 9689     | 0.06    | Candida krusei              |
| B. fragilis                      | 25285    | >32     | C. difficile                  | 17857    | 0.031   | Candida krusei              |
| Bacteroides ovatus               | 8483     | >32     | Clostridium perfringens       | 13124    | ≤0.015  | Candida glabrata            |
| Bacteroides uniformis            | 8492     | >32     | Enterococcus faecalis         | 19433    | 4       | Candida lusitaniae          |
| Campylobacter jejuni             | 29428    | 64      | Enterococcus faecium          | 19434    | 4       | Candida parapsilosis        |
| C. jejuni                        | 33291    | >64     | E. faecium                    | 49032    | 4       | Candida tropicalis          |
| C. jejuni                        | 49943    | 64      | E. faecium                    | 700221   | 4       | Candida tropicalis          |
| Citrobacter braakii              | 43162    | >64     | Lactobacillus acidophilus     | 4356     | >32     | E. faecium                  |
| Citrobacter freundii             | 43864    | >64     | Lactobacillus casei           | 393      | 1       | E. faecium                  |
| Enterobacter aerogenes           | 35028    | >64     | Lactobacillus rhamnosus       | 7469     | 16      | E. faecium                  |
| E. aerogenes                     | 13048    | >64     | Micrococcus luteus            | 381      | ≤0.125  | E. faecium                  |
| Enterobacter cloacae             | 49141    | >64     | M. luteus                     | 49732    | ≤0.125  | E. faecium                  |
| E. cloacae                       | 23355    | >32     | M. luteus                     | 533      | ≤0.125  | E. faecium                  |
| Escherichia coli                 | 26922    | >32     | M. luteus                     | 4698     | ≤0.06   | E. faecium                  |
| Fusobacterium nucleatum          | 25586    | >32     | Peptostreptococcus anaerobius | 27337    | ≤0.06   | E. faecium                  |
| Haemophilus influenzae           | 49247    | >32     | Peptostreptococcus (Peptoniphilus) asaccharolyticus | 29743 | 1       |
| Helicobacter pylori              | 43504    | >32     | Peptococcus (Finegoldia) magna | 29328 | 0.5 |
| Klebsiella oxytoca               | 43165    | >64     | Peptococcus (Micrococcus) micros | 33270 | 0.125 |
| K. oxytoca                       | 49131    | >64     | Propionibacterium acnes       | 11827    | 8       | E. faecium                  |
| Klebsiella pneumoniae            | 33495    | >64     | P. acnes                      | 6919     | 8       | E. faecium                  |
| K. pneumoniae                    | 27736    | >64     | Staphylococcus aureus         | 33591    | 8       | E. faecium                  |
| K. pneumoniae                    | 13883    | >32     | S. aureus                     | 25923    | 16      | E. faecium                  |
| Moraxella catarrhalis            | 25238    | 2       | S. aureus                     | 29213    | 8       | E. faecium                  |
| M. catarrhalis                   | 49143    | 1       | Staphylococcus epidermidis    | 12228    | 1       | E. faecium                  |
| Neisseria meningitidis           | 13077    | 64      | S. epidermidis                | 14990    | 1       | E. faecium                  |
| Neisseria gonorrhoeae            | 19424    | 8       | Staphylococcus intermedius    | 29663    | 4       | E. faecium                  |
| N. gonorrhoeae                   | 49226    | 32      | Streptococcus agalactiae      | 12386    | 16      | E. faecium                  |
| Neisseria lactamica              | 23970    | 32      | S. agalactiae                 | 13813    | 32      | E. faecium                  |
| Porphyromonas asaccharolytica     | 25260    | 32      | Streptococcus pyogenes        | 19615    | 16      | E. faecium                  |
| Prevotella loescheii             | 15930    | >32     | Streptococcus pneumoniae      | 49619    | >32     | E. faecium                  |
| Proteus mirabilis                | 25933    | >64     | Streptococcus sanguinis       | 10556    | 32      | E. faecium                  |
April 2007 showed that all *C. difficile* strains were susceptible to ≤1.0 μg/mL of fidaxomicin, with an MIC90 of 0.5 μg/mL.

**Clinical Trial In Vitro Susceptibilities**

Citron et al [9] reported the activity of fidaxomicin by REA type on *C. difficile* isolates recovered from the fidaxomicin phase II clinical trial for *C. difficile* infection. Thirty-eight of 49 enrolled subjects (78%) had a *C. difficile* organism isolated at baseline. Four subjects grew multiple colony types, with 1 of these subjects having 2 different REA-type strains. Fidaxomicin showed an MIC range of ≤0.008–0.125 μg/mL, with an MIC90 of 0.125 μg/mL. Samples from only 2 subjects who had a recurrence within 6 weeks of treatment yielded isolates with MICs within a dilution of those recovered at baseline. It was noted that the REA BI isolates had metronidazole and vancomycin, but not fidaxomicin, MIC90 values that were 2 dilutions higher than that for the non-BI strains.

Goldstein et al [10] reported the activity of fidaxomicin by REA type on 716 *C. difficile* isolates from 2 fidaxomicin phase III studies (Table 3). For all pretreatment isolates, the fidaxomicin MIC range was ≤0.004–1.0 μg/mL, with an MIC for inhibition of 50% of organisms (MIC50) of 0.125 μg/mL and an MIC90 of 0.25 μg/mL. Analyzed by REA type, 244 of 718 isolates (35%) were from the BI group, with MICs generally higher for all 4 drugs tested (MIC90: fidaxomicin, 0.5; vancomycin, 2.0; metronidazole, 2.0; and rifaximin >256 μg/mL) than for the other REA types. Fidaxomicin susceptibility of baseline isolates did not predict clinical cure, failure, or recurrence for fidaxomicin (baseline MIC90, 0.25 μg/mL [range, ≤0.008–1 μg/mL]). No resistance to fidaxomicin developed during treatment in either phase III study, although a single strain isolated from a cured patient had an elevated fidaxomicin MIC of 16 μg/mL at the time of recurrence.

Results of studies by Ackermann et al [4] and Credito and Applebaum [7] showing more potent activity of fidaxomicin against *C. difficile* than those of Karlowsky et al [8], Hecht et al [6], and Finegold et al [5] may have been related to the inclusion of higher numbers of clones with lower MICs. Although Credito and Applebaum [7] showed an MIC90 of 0.125 μg/mL, the MIC90 reported by Ackermann et al [4] was exceptionally low (0.008 μg/mL), which could alternatively be attributed to lower viability of cells when dimethyl sulfoxide (DMSO) was used as diluent and/or to use of an anaerobic environment with a higher carbon dioxide concentration (15% vs the CLSI-recommended 4%–7%), because carbon dioxide can acidify media.

**Effect of Diluent, pH, Inoculum, and Cations on Susceptibility**

Babakhani et al [12] found that variations in pH affected MICs. With use of both Brucella agar dilution and broth dilution methods, fidaxomicin MICs were unchanged between pH values of 6.2 and 7.0 but increased in a linear fashion and were 8-fold...
higher at pH values of 7.9–8.0. The organism was shown to grow poorly at a pH of 5.0. With use of the Wilkins-Chalgren broth microdilution method, Swanson et al [1] reported that the MICs of tiacumicin B against *C. difficile* American Type Culture Collection (ATCC) 9689 at pH values of 6.5 and 8.0 were unchanged or only 2-fold different from MICs determined at a pH of 7.3.

The effects of inoculum concentrations of $10^2$–$10^5$ colony-forming units/spot and of cation concentrations of calcium (at 33, 45, and 75 mg/L) or magnesium (21, 30, and 57 mg/L) were also studied [12]. Neither inoculum size nor cation concentration had an effect on fidaxomicin MICs for 2 reference *C. difficile* strains (ATCC 9689 and ATCC 700057) [12]. In contrast, as stated by the investigators, “vancomycin MICs increased progressively with increasing inoculum concentrations” [12, 2674–5]. Additionally, the investigators studied the effect of various commercial lots of media on MICs and reported no fidaxomicin MIC variation when tested with 3 different lots of commercially prepared supplemented Brucella agar media.

### Table 2. In Vitro Activity of Fidaxomicin, Compared With Vancomycin and Metronidazole, Against *Clostridium difficile* Isolates From 8 Published Studies

| Drug              | No. of isolates | Range          | MIC<sub>50</sub> (μg/mL) | MIC<sub>90</sub> (μg/mL) | [Ref] Year/sites |
|-------------------|-----------------|----------------|---------------------------|--------------------------|-----------------|
| Fidaxomicin       | 16              | 0.12–0.25      | 0.25                      | 0.25                     | [1] 1991/US     |
| Vancomycin        | 5–1             | 0.5            | 1                         |                          |                 |
| Metronidazole     | 0.12–0.5        | 0.25           | 0.5                       |                          |                 |
| Fidaxomicin       | 207             | ≤0.001–0.625   | 0.002                     | 0.008                    | [4] 2004/Europe |
| Vancomycin        | 0.016–0.5       | 0.5            | 0.5                       |                          |                 |
| Metronidazole     | 0.004–0.5       | 0.06           | 0.06                      |                          |                 |
| Fidaxomicin       | 23              | 0.06–2         | 0.12                      | 0.25                     | [5] 2004/US     |
| Vancomycin        | 0.5–4           | 1              | 2                         |                          |                 |
| Metronidazole     | 0.25–1          | 0.12           | 0.25                      |                          |                 |
| Fidaxomicin       | 208             | 0.06–1         | 0.25                      | 0.5                      | [8] 2008/Canada |
| Vancomycin        | 0.5–4           | 0.5            | 1                         |                          |                 |
| Metronidazole     | 0.25–4          | 0.5            | 1                         |                          |                 |
| Fidaxomicin       | 110             | 0.015–0.25     | 0.125                     | 0.125                    | [6] 1983–2004/US|
| Vancomycin        | 0.06–4          | 1              | 1                         |                          |                 |
| Metronidazole     | 0.025–0.5       | 0.125          | 0.25                      |                          |                 |
| Fidaxomicin       | 21              | ≤0.016–0.25    | 0.016                     | 0.12                     | [7] 2004/US     |
| Vancomycin        | 0.5–2           | 1              | 2                         |                          |                 |
| Metronidazole     | ≤0.125–0.5      | 0.25           | 0.5                       |                          |                 |
| Fidaxomicin       | 38              | ≤0.008–0.25    | ...                       | 0.125                    | [9] 2004–2005/US|
| Vancomycin        | 0.25–2          | ...            | 1                         |                          |                 |
| Metronidazole     | 0.25–2          | ...            | 1                         |                          |                 |
| Fidaxomicin       | 716             | ≤0.008–1       | 0.125                     | 0.5                      | [10] 2005–2010/US & Europe |
| Vancomycin        | 0.5–8           | 1              | 2                         |                          |                 |
| Metronidazole     | 0.02–4          | 0.5            | 1                         |                          |                 |

Abbreviations: MIC<sub>50</sub>, minimum inhibitory concentration for inhibition of 50% of organisms; MIC<sub>90</sub>, minimum inhibitory concentration for inhibition of 90% of organisms; US, United States.

### In Vitro Studies Against Enteric Flora

Ackermann et al [4] studied the activity of fidaxomicin against a limited number of eubacteria (26 isolates), lactobacilli (8), *Propionibacterium acnes* (16), *Prevotella* species (35), and *Bacteroides fragilis* (69) and found them generally not susceptible. MIC<sub>50</sub> and MIC<sub>90</sub> values were >128 μg/mL and >128 μg/mL, respectively, for *B. fragilis* and *Prevotella* species. Finegold et al [5] performed a more extensive study involving 453 intestinal bacteria and reported that streptococci, aerobic and facultative gram-negative rods, anaerobic gram-negative rods, and *Clostridium ramosum* were resistant, which might potentially be less disruptive to normal fecal flora. Against 50 isolates of the *B. fragilis* group, MIC<sub>50</sub> was 256 μg/mL and MIC<sub>90</sub> was >1024 μg/mL. They noted that fidaxomicin had activity against most clostridia, staphylococci, and enterococci.

Clinical results in support of these in vitro studies were seen in the fidaxomicin phase IIA dose-ranging trial, in which 30 patient stool samples cultured for normal flora [13] showed...
that B. fragilis group counts were not affected by increasing fidaxomicin dosages.

**OP-1118 In Vitro Activity**

OP-1118 is a major metabolite of fidaxomicin that also exhibits a narrow spectrum of activity. Tested in vitro by using CLSI susceptibility testing methods against 32 strains belonging to the commensal gastrointestinal flora, OP-1118 demonstrated activity against only some gram-positive organisms, with MICs 4–16-fold greater than those of fidaxomicin [14]. Similar to the parent compound, OP-1118 was not active against gram-negative bacteria.

We now report previously unpublished data regarding the in vitro activity of fidaxomicin and OP-1118 against 135 clinical strains of C. difficile isolated from patients in the 004 study who were compared by using the CLSI agar dilution method in M11-A7 [11]. An inoculum of $10^5$ colony-forming units/mL of C. difficile ATCC 700057 was included as a quality control strain. OP-1118 was dissolved and diluted in DMSO to achieve final study concentrations that ranged from 0.004 to 128 $\mu$g/mL. The MIC$_{50}$ and MIC$_{90}$ for OP-1118 were 4 and 8 $\mu$g/mL, compared with 0.125 and 0.25 $\mu$g/mL, respectively, for fidaxomicin (Figure 1).

**Low Fecal-Binding Properties**

The fecal-binding properties of fidaxomicin and OP-1118 were compared with those of vancomycin by testing their antibacterial activity in the presence or absence of 5% fecal material, using a microbroth dilution method. Similar to vancomycin, both fidaxomicin and OP-1118 demonstrated low fecal-binding properties, and their MICs against C. difficile increased only 4–8-fold in the presence of feces: the MIC of fidaxomicin increased from 0.25 to 2 $\mu$g/mL, and the MIC of OP-1118 increased from 1 to 4 $\mu$g/mL, with both increases much lower than the expected gut-level concentrations following oral administration of 400 mg/day of fidaxomicin [14].

**Killing Kinetics**

Fidaxomicin and its major metabolite, OP-1118, both demonstrate bactericidal activity against C. difficile strains, including the hypervirulent REA BI group strains. Exposure of C. difficile strains to fidaxomicin or OP-1118 at ≥4 times the MIC of each agent led to a ≥3 log decrease in colony-forming units in 48 hours, indicating time-dependent bactericidal activity [15]. Interestingly, fidaxomicin has been shown to be bactericidal against laboratory-generated mutant strains with reduced fidaxomicin susceptibility, indicating that with fecal concentrations that reach milligram-per-gram amounts, even mutant strains with increased fidaxomicin MICs are likely to be killed during therapy [15].

**Susceptibility Breakpoints/Resistance**

Results from fidaxomicin clinical trials have not demonstrated a correlation between MIC and clinical outcome [10, 16]. Although the MIC$_{90}$ was shown to be 0.25 $\mu$g/mL in these trials, the highest reported MIC for wild-type isolates is 1 $\mu$g/mL. The only clinical isolate with reduced susceptibility was obtained from a subject with recurrence of disease 6 days following cure with fidaxomicin. The isolate at day 1 and the end of treatment had an MIC of 0.06 $\mu$g/mL, but the recurrence isolate demonstrated reduced susceptibility, with an MIC...
of 16 μg/mL, which is still less than gut-level concentrations of the drug (mean fidaxomicin and OP-1118 concentrations were reported as 1433 and 760 μg/g, respectively) [16]. The strain with reduced susceptibility has been analyzed further, and a single mutation in the β subunit of the RNA polymerase has been identified in only the isolate associated with recurrence (unpublished data). Similar mutations in the homologous positions in other bacterial species that demonstrate reduced susceptibility to lipiarmycin, a related macrocycle compound, have been reported [17, 18]. However, the functional significance of such mutations needs to be elucidated further because laboratory-generated isolates with similar mutations are rapidly killed by fidaxomicin at 4 times the MICs [15].

CONCLUSION

Fidaxomicin has excellent in vitro activity against C. difficile isolates of all REA types, including the epidemic BI strain. Resistance has not developed during therapy in clinical trials. Its lack of activity against enteric gram-negative flora should help maintain colonization resistance.

Notes

Acknowledgments. We thank Judee H. Knight and Alice E. Goldstein for various forms of assistance.

Supplement sponsorship. This article was published as part of a supplement entitled “Fidaxomicin and the Evolving Approach to the Treatment of Clostridium difficile Infection,” sponsored by Optimer Pharmaceuticals, Inc.

Potential conflicts of interest. E. J. C. G. serves on the advisory boards of Merck, Optimer, Bayer Pharmaceuticals, Theravance, BioK+, and Viropharma, Kindred Healthcare; is on the speakers bureau of Bayer, Merck, Sanofi Pasteur, and Forest Labs; and has received research grants from Merck, Schering-Plough Pharmaceuticals, Optimer Pharmaceuticals, Theravance, Cubist, Pfizer, Astellas, Cerexa, Impex Pharmaceuticals, Novexel, Novartis, Clinical Microbiology Institute, Genzyme, Nanopacific Holdings, Romark Laboratories, Virosis, Warner Chilcott, Avidiotics, GLSynthesis, Immunome, Toltec Pharma, and Salix Pharmaceuticals, GSK. F. B. is an employee of Optimer Pharmaceuticals. D. M. C. certifies no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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