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Safety and Efficacy of Fidaxomicin in Patients With *Clostridium Difficile* Infection

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Abstract: Fidaxomicin is a bactericidal macrolide that is indicated for the treatment of *Clostridium difficile* infection (CDI) in adults. Fidaxomicin is not effective for the treatment of systemic infections due to minimal systemic absorption. Until recently, oral vancomycin was the only medication with United States Food and Drug Administration (FDA) approval for the treatment of CDI. In clinical studies, fidaxomicin demonstrated noninferiority to vancomycin for the treatment of CDI. Lower recurrence rates of CDI with fidaxomicin than with oral vancomycin were observed. The lower recurrence rates were not observed with highly virulent strains of *C. difficile*. Lower recurrence rates of CDI with fidaxomicin are believed to be associated with its narrow spectrum of activity. Fidaxomicin was approved for use after publication of the most recent guideline from the Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA). However, its current place in clinical practice is unknown. The cost of fidaxomicin should be considered when prescribing this medication.

Keywords: fidaxomicin, treatment, safety, efficacy, *Clostridium difficile*, infection, CDI

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Introduction

The major cause of antibiotic-associated diarrhea is *Clostridium difficile*. *C. difficile* infection (CDI) can range in severity from uncomplicated diarrhea to pseudomembranous colitis to death. *C. difficile* is a ubiquitous, Gram-positive anaerobic, spore-forming bacillus implicated in 15% to 25% of cases of antibiotic-associated diarrhea, 50% to 70% of cases of antibiotic-associated colitis, and >90% of cases of antibiotic-associated pseudomembranous colitis.¹⁻⁴ CDI occurs when normal gut flora is disrupted, allowing overgrowth of native or newly acquired *C. difficile*. Toxin produced by *C. difficile* binds to receptors on intestinal epithelial cells resulting in mucosal injury and inflammation. Virtually all classes of antibiotics have been implicated in causing CDI with broad-spectrum agents having the highest risk.⁵

Oral vancomycin has been the only medication with United States Food and Drug Administration (FDA) approval for the treatment of CDI. Based on current Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) guidelines, oral metronidazole is considered first-line therapy for mild to moderate CDI.⁶ This is due to metronidazole's comparable effectiveness and lower cost compared with oral vancomycin. Oral vancomycin is typically reserved for patients with severe CDI or those who cannot tolerate or fail therapy with metronidazole. Combination therapy with both metronidazole and oral vancomycin is used for severe, complicated infections.⁶

Fidaxomicin is now the second drug approved by the FDA for treatment of CDI in adults (≥ 18 years of age).⁷ Additionally, the FDA has provided orphan drug approval for use in pediatric patients, but data in this population are limited. Fidaxomicin is a macrolide that is bactericidal for *Clostridium difficile*. Effectiveness of the agent is limited to the gastrointestinal tract, and it is not effective for the treatment of systemic infections due to minimal systemic absorption.⁷

Mechanism of Action of Fidaxomicin

Mechanism of action

The structure of fidaxomicin includes an unsaturated 18-membered macrocyclic core. It is isolated from a strain of the bacterium *Dactylosporangium aurantiacum* and is a member of the tiacumicin family.⁷

Fidaxomicin inhibits bacterial protein synthesis by binding to RNA polymerase.⁷ The bactericidal activity against *C. difficile* is followed by a post-antibiotic effect of 6–10 hours for fidaxomicin and 3 hours with OP-1118, its active metabolite.^{7,8}

Mechanism of resistance

In vitro, there is a low frequency of spontaneous resistance to fidaxomicin in *Clostridium difficile*. During clinical trials, a patient with recurrent CDI was noted to have a specific mutation (Val-1143-Gly) in the RNA polymerase beta subunit. This mutation conveys reduced susceptibility to fidaxomicin.⁷

Antimicrobial Activity of Fidaxomicin

Spectrum of activity

Fidaxomicin is a narrow-spectrum antibiotic that demonstrates activity against Gram-positive aerobic and anaerobic bacteria, specifically *Clostridia* species. Fidaxomicin has no activity against Gram-negative pathogens. Fidaxomicin spares predominant members of the gut normal flora, minimizing disruption.^{9,10} This narrow spectrum of activity may explain the lower rates of recurrent CDI. In addition, lower spore counts following therapy with fidaxomicin when compared with vancomycin have been observed.¹¹

Pharmacokinetics of Fidaxomicin

Fidaxomicin has minimal systemic absorption. In phase one clinical studies, healthy volunteers received oral Fidaxomicin 100, 200, 300, and 450 mg with plasma concentrations that were low to undetectable.¹² Fidaxomicin is mainly confined to the gastrointestinal tract with fecal concentrations more than 10,000 times the plasma concentration. Metabolism of fidaxomicin occurs in the intestine via hydrolysis and does not depend on CYP450 enzymes. OP-1118 is fidaxomicin's main active metabolite. Excretion of fidaxomicin is mainly in the feces (>92% unchanged drug and active metabolite) with <1% recovered from the urine.⁷ Adult dosing of fidaxomicin is 200 mg orally twice daily for 10 days.⁷

Efficacy of Fidaxomicin against *Clostridium Difficile* Infections

Two multicenter phase III trials of fidaxomicin have been completed. Both were randomized,



double-blinded, noninferiority studies. Each study evaluated fidaxomicin 200 mg given orally twice daily for 10 days versus oral vancomycin 125 mg four times daily for 10 days in adults with CDI. The North American phase III trial enrolled 629 adult patients, and the international trial, 535 patients.^{13,14}

In the North American trial conducted in the United States and Canada, the primary end point of noninferiority was met. No significant differences were noted with subgroup analyses of rates of clinical cure according to the patient's age, inpatient versus outpatient status, prior occurrence of *C. difficile* infection versus no prior occurrence, treatment for *C. difficile* infection versus no treatment within 24 hours before the start of the study, baseline severity of disease, infecting strain type, no response versus response to previous metronidazole therapy, and use versus nonuse of concomitant systemic antimicrobial therapy. Treatment with fidaxomicin was associated with a significantly lower rate of recurrence than with vancomycin. The relative risk of recurrence for patients with non-NAP1/BI/027 strain was approximately 3.3 times higher (95% CI, 1.6 to 6.9) among patients receiving vancomycin versus fidaxomicin. Overall recurrence was 13.3% and 24% ($P < 0.01$) of patients who were given fidaxomicin and vancomycin. Rates of recurrence were similar among patients with the NAP1/BI/027 strain.^{13,14}

In the international phase III trial, clinical cure rates, defined as resolution of symptoms and no further need for CDI therapy, were similar for fidaxomicin and oral vancomycin. Global cure in this study was defined as clinical cure with no recurrence. Global cure was higher for fidaxomicin than for vancomycin, 79.6% (172/216 patients) versus 65.5% (154/235 patients), respectively ($P < 0.001$). Recurrence of CDI was defined as diarrhea and positive stool toxin test within 4 weeks after treatment. A statistically significant lower rate of recurrence was seen in the fidaxomicin group versus the vancomycin group. No difference in clinical cure or global cure was observed in patients with NAP1/BI/027 strain.¹⁴

The combined results on clinical cure, recurrence, and global cure rates from both phase III trials showed that fidaxomicin was noninferior to vancomycin.¹⁵ No statistically significant differences were observed in patients with BI/NAP1/027 strain in cure rate and recurrence rate for fidaxomicin versus

vancomycin in the combined phase III results.¹⁶ The BI/NAP1/027 strain has been reported in outbreaks of CDI in health care facilities and is associated with more antibiotic resistance and more severe disease.¹⁷

Adverse Effects

The safety of fidaxomicin was evaluated in 564 patients of whom 86.7% received a full course of treatment. A remarkably low withdrawal rate of 5.9% (33 patients) due to adverse reactions was observed. Vomiting was the primary adverse reaction leading to discontinuation of the drug. Nausea was the most common adverse reaction reported at 11%.⁷ Adverse effects with vancomycin therapy demonstrated no significant differences in the phase III North America Trial. Nausea with fidaxomicin was reported at a rate of 10.3% and with vancomycin a rate of 8.7%.¹³ It is difficult to distinguish these side effects from symptoms as both are commonly present with CDI.

Safety of fidaxomicin

Animal studies have not revealed significant toxicity associated with the administration of fidaxomicin. The 50% lethal dose was greater than 200 mg/kg when administered to rats intravenously, and no adverse effects were noted in rats administered oral fidaxomicin up to 1000 mg/kg.¹⁸ No cases of acute overdose have been reported in humans. No drug-related adverse effects were seen in dogs dosed with fidaxomicin tablets at 9600 mg/day for three months, over 100 times the therapeutic human dose.⁷ No drug-drug interactions have been reported with this medication or its active metabolite OP-1118.¹⁹

Special populations

Fidaxomicin is pregnancy category B. Reproduction studies have been performed in rats and rabbits by the intravenous route at doses up to 12.6 and 7 mg/kg, respectively. The plasma exposures were approximately 200- and 66-fold that in humans, and revealed no evidence of harm to the fetus. There are no adequate, well-controlled studies in pregnant women. It is not known whether fidaxomicin is excreted in human milk.⁷ The safety and efficacy of fidaxomicin in patients < 18 years of age has not been established.⁷ The manufacturer of fidaxomicin has been granted orphan drug designation for the treatment of pediatric CDI, but data for use in this population are lacking.²⁰



Of the patients in controlled trials, 50% were 65 years of age and older, while 31% were 75 and older. No overall differences in safety or effectiveness were observed.⁷

Fiscal Impact

Insurance companies are classifying fidaxomicin as a tier three medication and will likely require prior authorization with documentation of failure with traditional therapies. Expected retail cost for a 10-day course of fidaxomicin is reported as \$3250.²¹ Optimer currently offers a patient assistance program for the uninsured and underinsured. The application process requires information regarding income and insurance.²² Upon completion of the application process, fidaxomicin will be made available to eligible patients for the duration of their therapy.

Conclusion

Fidaxomicin represents a unique tool in the treatment of CDI. Its narrow spectrum of activity and low rate of side effects are distinct advantages for its efficacy and safety. The rate of CDI recurrence favors fidaxomicin in non-NAP1/BI/027 strain infections when compared with conventional therapies. Cost of fidaxomicin is likely to govern its role in the treatment of CDI in the near term. Postmarketing research and pharmacoeconomic analysis are necessary to provide further guidance for its role in CDI treatment.

Author Contributions

Wrote the first draft of the manuscript: MD, CC, JD. Contributed to the writing of the manuscript: MD, CC, JD. Agree with manuscript results and conclusions: MD, CC, JD. Jointly developed the structure and arguments for the paper: MD, CC, JD. Made critical revisions and approved final version: MD, CC, JD. All authors reviewed and approved of the final manuscript.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

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