New Drug

Fidaxomicin: The Newest Addition to the Armamentarium Against *Clostridium difficile* Infections

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ABSTRACT

Background: Fidaxomicin, a macrolide antibiotic, was the first medication for the management of *Clostridium difficile* infections (CDI) to be approved by the US Food and Drug Administration in more than 20 years.

Objective: This article reviews published literature on fidaxomicin for management of CDI, including its chemistry, spectrum of activity, pharmacokinetic properties, pharmacodynamics, therapeutic efficacy, adverse events, dosing, administration, and pharmacoeconomic considerations.

Methods: Pertinent English-language literature was reviewed through searches of MEDLINE, EMBASE, and BIOSIS from 1975 through September 2011. Reference lists of identified publications and published abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy meetings were also reviewed. Search terms included, but were not limited to, *fidaxomicin*, *difimicin*, *lipiarmycin*, *tiacumicin B*, *OPT-80*, *Clostridium spp*, and *diarrhea*.

Results: A total of 79 publications were identified and 10 were excluded; 6 review articles and 4 abstracts that were later published as articles. Fidaxomicin's in vitro profile is favorable compared with oral metronidazole and vancomycin, with minimum inhibitory concentrations against *C difficile* that are 2 dilutions lower. From the 2 published Phase III trials, fidaxomicin was deemed to be noninferior in the treatment of mild to moderate CDI compared with oral vancomycin. Recurrence rates for all strains of CDI were lower with fidaxomicin than vancomycin. Adverse events associated with fidaxomicin were similar to placebo, with nausea and vomiting being the most common.

Although no pharmacoeconomic studies have compared fidaxomicin with metronidazole or vancomycin, the current price exceeds $2500 (US) per treatment course.

Conclusions: Reports suggest that fidaxomicin is noninferior to oral vancomycin in the treatment of mild or moderate CDI, although no published comparisons with metronidazole exist to date. Additionally, fidaxomicin improved outcomes compared with oral vancomycin in terms of rates of relapse and recurrent CDI, and in patients who might require concomitant antibiotics. Prospective, randomized studies comparing fidaxomicin with metronidazole in the treatment of mild or moderate CDI, as well as against vancomycin for severe CDI, should be undertaken to clarify the exact role of fidaxomicin in clinical practice. (*Clin Ther*. 2012;34:1–13)

Key words: *Clostridium* spp, diarrhea, fidaxomicin, treatment.

INTRODUCTION

Fidaxomicin* is the latest addition in the armamentarium against *Clostridium difficile* infections (CDI). Fidaxomicin is only available for use within the United States at this time, and was approved by the US Food and Drug Administration (FDA) on May 27, 2011.[1] Fidaxomicin joins vancomycin as the only other medication approved by the FDA for this indication.

C difficile, a gram-positive, anaerobic, spore-forming bacilli, is responsible for a large number of infections, including several epidemics throughout North America and Europe.[2–7] *C difficile* has been implicated in a variety of gastrointestinal (GI) infections, ranging

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from asymptomatic colonization and mild diarrhea to pseudomembranous colitis, intestinal perforation, toxic megacolon, and death.[8–10] *C difficile* is the causative pathogen in up to 25% of all antibiotic-associated diarrhea, and has been estimated to infect 2% of all hospitalized patients and up to 4% of those in an intensive care unit.[4,11–16] Based on US data from the National Inpatient Sample,[17] the incidence and mortality of CDI in hospitalized patients nearly doubled in a 5-year period from 2000 to 2005. It has been estimated that the annual care and treatment of CDI exceeds $3 billion dollars in the United States (2007 US dollars).[3,18]

In addition, a recently identified hypervirulent strain of *C difficile*, specifically the North American Pulsed Field type 1 (NAP1), restriction endonuclease analysis type BI, or polymerase chain reaction ribotype 027, jointly known as the NAP1/BI/027 strain, has been implicated as a causative factor of CDI outbreaks.[4,19] The NAP1/BI/027 strain of *C difficile* has been deemed "hypervirulent" for its ability to produce binary toxin *C difficile* 126 adenosine diphosphate-ribosyltransferase (CDT) (actin-specific ADP-ribosyltransferase) not typically found in other strains of *C difficile*, combined with its ability to produce excessive quantities of enterotoxins A and B, compared with other strains of *C difficile*.[4,19–21] In some reports, patients infected with the NAP1/BI/027 strain of *C difficile* have been classified as having more severe disease based on the need for colectomy, intensive care unit stay, or death attributable to CDI when compared with those infected with non-NAP1/BI/027 strains. However, recent literature suggests there might be no difference in patient outcomes based on the causative strain of *C difficile*.[6,19–22]

Treatment guidelines jointly published in 2010 by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America[23] provide clinicians with recommendations for the management of CDI in adult patients. From these guidelines, the recommended agents against CDI are oral metronidazole (mild to moderate disease) and oral vancomycin (severe disease). At the time of publication, only vancomycin carried FDA approval for treatment of CDI.[24]

Because of the favorable cost profile for metronidazole compared with vancomycin, metronidazole has long been the preferred treatment modality for mild to moderate CDI, for both first occurrences and first recurrences.[23] For severe CDI as well as for those infections caused by the NAP1/BI/027 strain of *C difficile*, metronidazole has shown less favorable outcomes when compared with vancomycin,[25,26] with cure rates reported to be as low as 76% and recurrence rates reported to be as high as 27%.[26,27] Several theories have been provided for this, including reduced susceptibility of metronidazole against the NAP1/BI/027 *C difficile* strain[28] and increased absorption of metronidazole within the proximal intestine, leading to decreased fecal concentration.[7] Currently, empiric treatment of severe CDI with oral vancomycin is recommended.[23] However, use of oral metronidazole or vancomycin, especially vancomycin, has been reported to select for resistant bacteria, namely methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci (VRE) when administered by oral route.[29,30]

To try and combat the increasing rates of treatment failure, emergence of outbreaks caused by the hypervirulent NAP1/BI/027 strain of *C difficile*, and selection of resistant bacteria in the GI tract, and to reduce rates of recurrence, several new agents are under investigation for the treatment of CDI, including nitazoxanide, rifaximin, tigecycline, and intravenous immune globulin.[31–38] Fidaxomicin is the first FDA-approved antibiotic for the treatment of CDI in more than 20 years.[1] The available literature surrounding the role of fidaxomicin in the management of antibiotic-associated CDI will be discussed here, with particular focus on, but not be limited to, its chemistry, mechanism of action, pharmacology, pharmacodynamics, published clinical studies, and place in therapy.

METHODS

Pertinent English-language literature was identified and evaluated through electronic literature searches of MEDLINE, EMBASE, and BIOSIS from the year 1975 through September 2011. Search terms included, but were not limited to, *fidaxomicin*, *difimicin*, *lipiarmycin*, *tiacumicin B*, *PAR-101*, *OPT-80*, *Clostridium spp*, *diarrhea*, and *pseudomembranous colitis*. Additional publications were identified by reviewing the reference lists of those publications found as a result of the literature searches, reviewing abstracts from meetings of the Interscience Conference on Antimicrobial Agents and Chemotherapy (2004–2010), as well as through correspondence with the manufacturer.