Fidaxomicin: a new option for the treatment of \textit{Clostridium difficile} infection

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The two drugs currently recommended for the treatment of \textit{Clostridium difficile} infection (CDI), namely vancomycin and metronidazole, are both associated with high rates of recurrence of infection. Hence there is a need for new treatment options. The novel oral macrocyclic antibiotic fidaxomicin (previously known as PAR-101, OPT-80 and difimicin) was recently approved in the USA and in Europe for the treatment of CDI. Clinical trials have shown non-inferiority with regard to clinical cure when compared with oral vancomycin, and reduced rates of recurrence of infection, with a concomitant increase in the overall rate of sustained response, although improved sustained response was not seen in the sub-group of patients infected with the \textit{C. difficile} NAP1/B1/027 strain. The introduction of fidaxomicin extends the options for the treatment of CDI and may help to reduce the burden of this disease if fewer patients have recurrence of infection.

**Keywords:** antibiotic-associated diarrhoea, OPT-80, macrocyclic antibiotic

**Introduction**

The Gram-positive spore-forming bacillus \textit{Clostridium difficile} is a leading cause of antibiotic-associated diarrhoea in hospitals and long-term care facilities in many countries around the world.\textsuperscript{1} Although the incidence of \textit{C. difficile} infection (CDI) has declined in England in recent years, there were still >18000 reported cases during the 2011–12 financial year.\textsuperscript{2} In addition to its clinical impact on patients, CDI has a significant economic impact on healthcare systems, with data from the USA showing reported costs of US$10212–13675 per infected patient and a mean increase in length of hospital stay of 3–6.4 days.\textsuperscript{3–5} Economic data from Europe indicated that the incremental costs associated with cases of CDI were £4577 in Ireland and £8843 in Germany, after standardization to 2010 prices.\textsuperscript{6}

The initial management of patients with CDI should, if possible, involve discontinuation of any antibiotics that may have precipitated its onset by disrupting the normal microbial ecology of the large intestine, allowing \textit{C. difficile} to establish itself and cause toxin-mediated disease. If this fails, oral treatment with either metronidazole or vancomycin should be initiated, with vancomycin being superior in cases of severe CDI.\textsuperscript{7} However, CDI is characterized by high rates of longer-term treatment failure, with \approx 20\% of patients experiencing recurrence following resolution of a first episode of CDI.\textsuperscript{8} In addition, the use of these drugs is not ideal, with both potentially selecting for emergence of glycopeptide-resistant enterococci in the gut, while use of metronidazole may induce side effects such as nausea, neuropathy or leucopenia.\textsuperscript{9} An added concern is the recent emergence of strains of \textit{C. difficile} with reduced susceptibility to metronidazole,\textsuperscript{10} which raises issues with regard to the future efficacy of this agent in the treatment of CDI.\textsuperscript{11} It is therefore clear that there is an urgent need for new treatment options for infection with \textit{C. difficile}. The remainder of this review focuses on fidaxomicin, a new antibiotic specifically developed and recently approved in the USA and Europe for the treatment of CDI.

**Mode of action and \textit{in vitro} activity**

Fidaxomicin (previously known as PAR-101, OPT-80 and difimicin) is a novel macrocyclic antibiotic comprising an 18-membered core with a 7-carbon sugar at position 12 and a C-6 deoxysugar at position 21 (Figure 1), produced by the fermentation of \textit{Dactylosporangium aurantiacum}.\textsuperscript{12} Based on research with a related compound, lipiarycin, it is postulated that fidaxomicin inhibits bacterial RNA synthesis by binding to and inhibiting the action of DNA-dependent RNA polymerase. Although its detailed mode of action remains to be fully elucidated, fidaxomicin apparently targets the initiation of RNA synthesis at an earlier stage than rifamycins.\textsuperscript{13} Fidaxomicin has a narrow spectrum of antibacterial activity \textit{in vitro}, encompassing Gram-positive bacteria including \textit{C. difficile}. MIC\textsubscript{90} values for clinical isolates of \textit{C. difficile} are typically in the range 0.008–0.25 mg/L, about three orders of magnitude lower than human gut concentrations of fidaxomicin.\textsuperscript{14–21} Furthermore, fidaxomicin is bactericidal for \textit{C. difficile}, with a 3 log\textsubscript{10} decrease in viable count seen over 24 h, and also exhibits a prolonged (>24 h) post-antibiotic
omicin has been associated with lower post-treatment recurrence possibly explaining reduced recurrence rates is that fidaxomycin, likely by gut colonization with pathogens such as *C. difficile*, will be important in maintaining colonization resistance, which bacilli that comprise a component of the normal gut flora may in the gut lumen. 24 Follow-up studies in cynomolgus monkeys of oral administration, fidaxomicin was not absorbed but remained oral doses of 30 and 90 mg/kg being 50–85 and 120–420 ng/mL, respectively. 25

The pharmacokinetics of fidaxomicin were subsequently assessed in two Phase 1 clinical studies in which healthy volunteers received oral doses of 100, 200, 300 and 450 mg. 26 In both studies there was minimal absorption of fidaxomicin from the gut, as evidenced by high recovery of unchanged drug or its major metabolite (OP-1118) in faeces, while the concentrations of fidaxomicin in plasma were generally low, often below the lower limit of quantification (5 ng/mL). It was reported that no appreciable levels of fidaxomicin were found in urine, which was thought to be consistent with low absorption into plasma. In the first Phase 1 study (a dose escalation study in which volunteers received single doses with a 1–2 week washout interval separating the treatments) the total faecal recovery of parent drug plus OP-1118 from patients receiving 200–300 mg doses was recorded as 116 ± 47.1%; the authors suggested that values >100% may have been due to non-homogeneity of the faecal samples. Faecal recovery in the patients receiving doses of 110 or 450 mg was not assessed due to incomplete faecal collection from these groups. 25

**Pharmacokinetics and metabolism**

Initial studies in Golden Syrian hamsters indicated that, following oral administration, fidaxomicin was not absorbed but remained in the gut lumen. 24 Follow-up studies in cynomolgus monkeys using sensitive assays also showed minimal intestinal absorption, the *C*max value of fidaxomicin in the plasma of animals receiving oral doses of 30 and 90 mg/kg being 50–85 and 120–420 ng/mL, respectively. 25

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In the second Phase 1 study (a multidose, dose escalation study), faecal concentrations were higher than in the single-dose study, with the increases appearing to be dose-related. Similar results, with low plasma levels and high faecal concentrations, were seen in subsequent Phase 2 and 3 trials, with the faecal concentrations of fidaxomicin exceeding the MIC90 value for *C. difficile* by 2000- to 10000-fold with increasing dosages. 27,28

**Clinical efficacy**

In an initial open-label Phase 2 dose evaluation trial, patients with mild to moderate CDI (either a primary episode or first recurrence) received 50, 100 or 200 mg of fidaxomicin orally every 12 h (corresponding to 100, 200 or 400 mg/day) for 10 days. 27 Based on resolution of diarrhoea by day 10, the clinical cure rates were 71%, 80% and 94% for the three patient groups, which comprised 14, 15 and 16 patients, respectively. A further two patients who received 100 mg/day (14%), one who received 200 mg/day (7%) and one who received 400 mg/day (6%) also showed resolution of diarrhoea after day 10 with no additional treatment. 27 Treatment failure was seen in four patients (8.9% of the study population), of whom two received 100 mg/day and two received 200 mg/day, although none of the four remained culture-positive for *C. difficile*, and only one (in the 200 mg/day group) remained toxin-positive. Recurrence was noted after ~4 weeks in 2 of the 41 patients clinically cured. 27

Based on the results from the above trial, two Phase 3 trials were carried out in which patients with CDI were randomized to receive either 200 mg of fidaxomicin taken orally twice daily or 125 mg of vancomycin taken orally four times a day for 10 days. 26,28 In the first trial patients were enrolled from 52 sites in the USA and 15 sites in Canada. 28 As the distribution of strains of *C. difficile* is known to vary geographically, the second trial recruited patients not only from sites in Canada and the USA (n=41) but also from 45 sites in Europe. 29 The trials were otherwise identical in terms of design and procedures. A total of 1164 patients were enrolled (629 and 535 in trials 1 and 2, respectively), with 1147 patients receiving one or other study drug (583 received vancomycin and 564 received fidaxomicin). In each trial the primary endpoint was clinical cure, defined as the resolution of diarrhoea, this being maintained for the duration of therapy with no further need for treatment (decided by the physician) as of the second day after the last dose of study drug. The secondary endpoints were recurrence of CDI during the 4 week period after treatment and global cure (i.e. cures with no recurrence, also referred to as sustained clinical response). 20

In both trials the rates of clinical cure in patients who received fidaxomicin were noninferior to those seen in patients who received vancomycin (Table 1). In addition, there were significantly fewer recurrences of infection among the patients who received fidaxomicin than among those treated with vancomycin; the corollary of this was that there was a higher rate of sustained response in the patients receiving fidaxomicin (Table 1). Interestingly, however, a sub-analysis showed that the overall clinical cure rate in patients infected with the NAP1/B1/027 strain of *C. difficile* (widely regarded as a hyper-virulent strain) was lower (86.6%) than the cure rate seen in patients infected with other strains (94.3%), irrespective of the study.
drug used for treatment. Similarly, there was a higher rate of recurrence of CDI in patients infected with the NAP1/B1/027 strain (27.4%) than in patients infected with other strains (16.6%). Thus, the significantly lower overall recurrence rate seen in fidaxomicin recipients was not present in the sub-group of NAP1/B1/027 cases. Another finding of note arising from sub-analysis was that concomitant use of antibiotics for other indications in patients receiving treatment for CDI was associated with a lower cure rate (84.4% versus 92.6% in patients not receiving concomitant antibiotics) and an extended time to resolution of diarrhoea (97 versus 57 h). However, among the patients receiving concomitant antibiotics, the clinical cure rate in patients who received fidaxomicin (90%) was significantly higher than that seen in patients who received vancomycin (79.4%; \( P=0.04 \)). In addition, among patients receiving concomitant antibiotics, treatment of CDI with fidaxomicin was associated with 12.3% fewer recurrences (16.9% versus 29.2%; \( P=0.048 \)).

**Patient safety**

During the Phase 3 clinical trials, patient safety was assessed by physical examination, electrocardiography and a range of clinical laboratory tests. There were no significant differences in the overall rates of treatment-emergent or serious adverse events seen in patients receiving fidaxomicin compared with those occurring in vancomycin recipients. Gastrointestinal disorders were the most commonly reported events (28.4% versus 27.4% of patients receiving fidaxomicin and vancomycin, respectively), followed by infections (20.6% versus 18.5%) and general disorders such as pyrexia, chills, fatigue or pain (14.7% versus 17.3%). The rate of serious adverse events was <3% and did not differ between the two patient groups.

**Discussion**

The management of CDI has long been problematic, with treatment being limited to vancomycin or metronidazole as first-line options, and use of either drug being associated with high rates of recurrence of infection. The recent approval of the new macrocyclic antibiotic fidaxomicin thus offers a potentially significant advance in the management of CDI, particularly with regard to reducing the numbers of patients who suffer recurrences of infection. This in turn should help reduce the numbers of patients in hospital with CDI who, by the very nature of their disease (which results in contamination of the local environment with spores), act as potential sources of cross-infection for other patients. However, the clinical trials to date have been restricted to patients suffering a first episode (primary occurrence) or first recurrence of CDI and further research is required to determine the effectiveness of fidaxomicin in patients with multiple recurrences. In addition, patients with life-threatening or fulminant CDI or toxic megacolon were excluded from the trials, and so clinical experience of the use of fidaxomicin in these settings is still lacking.

A problem facing all new antibiotics following their license for clinical use is whether their efficacy will be compromised by the emergence and spread of strains of resistant bacteria. The MIC\(_{90}\) of fidaxomicin is typically 0.25 mg/L, and given that local concentrations of the drug in faeces following oral administration exceed this value by up to 10000-fold, it seems intuitively that resistance is unlikely to arise, particularly given the drug’s bactericidal activity and prolonged post-antibiotic effect. However, in the Phase 3 clinical trials, one patient who had a baseline isolate of *C. difficile* with a fidaxomicin MIC of 0.06 mg/L suffered a recurrence 6 days after the last dose of fidaxomicin, and sampling at this time yielded an isolate with a fidaxomicin MIC of 16 mg/L (i.e. a 256-fold increase in MIC). Hence surveillance of the susceptibility of *C. difficile* to fidaxomicin should be a research priority, particularly in areas where the NAP1/B1/027 strain, which was associated with lower rates of clinical cure, is commonly isolated.

Although fidaxomicin seems an attractive option for the treatment of CDI, its uptake in clinical practice may be limited if the cost appears prohibitive, at least in relation to the costs of vancomycin or metronidazole, the current first-line drugs. One way forward is to target fidaxomicin usage in patients with CDI who are at increased risk of recurrence. Reported risk factors for recurrent CDI include previous CDI, age >65 years, severe disease, receipt of concomitant antibiotics, emergency hospital admission, previous admission specialty and duration of hospital stay. Translating such risk factors into clinical practice, e.g. via a risk score, should be encouraged. A health economic evaluation of the cost-effectiveness of the use of fidaxomicin versus current treatment options would therefore seem to be another priority for research. In this way, not only the clinical benefits to patients but the economic benefit (or otherwise) to healthcare providers will allow the formulation of rational and cost-effective guidance for the treatment of CDI.

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**Table 1. Outcomes in two clinical trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>mITT</th>
<th>per protocol</th>
<th>mITT</th>
<th>per protocol</th>
<th>mITT</th>
<th>per protocol</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>fidaxomicin</td>
<td>88.2</td>
<td>92.1</td>
<td>15.4</td>
<td>13.3</td>
<td>74.6</td>
<td>77.7</td>
</tr>
<tr>
<td>1</td>
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<td>89.8</td>
<td>25.3</td>
<td>24.0</td>
<td>64.1</td>
<td>67.1</td>
</tr>
<tr>
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<td>91.7</td>
<td>12.7</td>
<td>12.8</td>
<td>76.6</td>
<td>79.6</td>
</tr>
<tr>
<td>2</td>
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<td>90.6</td>
<td>26.9</td>
<td>25.3</td>
<td>63.4</td>
<td>65.5</td>
</tr>
</tbody>
</table>

mITT, modified intention-to-treat.
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