Clostridium difficile infection: fidaxomicin

Evidence summary
Published: 13 July 2012
nice.org.uk/guidance/esnm1

Overview

Key points from the evidence

The content of this evidence summary was up-to-date in July 2012. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Fidaxomicin (Dificlir) is the first in a new class of macrocyclic antibiotics and has recently been licensed by the European Medicines Agency (EMA) for the treatment of Clostridium difficile infection (CDI). Current Health Protection Agency (HPA) guidance recommends metronidazole as first-line therapy in mild to moderate CDI, but vancomycin in severe cases. Fidaxomicin has not been compared to metronidazole in clinical trials.

Evidence from two double-blind, randomised controlled trials indicates it is non-inferior to vancomycin in curing patients with mild to severe CDI. Its side-effect profile appears similar to that of oral vancomycin and it may have advantages in reducing the rate of recurrence.

When considering the use of fidaxomicin, local decision makers should take into account the potential benefits alongside the medical need, the risks of treatment, and the relatively high cost of fidaxomicin in comparison with other treatments for CDI.
About this evidence summary

‘Evidence summaries: new medicines’ provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

Relevance to NICE guidance programmes

Fidaxomicin was not considered appropriate for a NICE technology appraisal and is not currently planned within any other NICE work programme.

Introduction

Clostridium difficile infection\(^1\) (CDI) is the most important cause of hospital-acquired diarrhoea. CDI ranges from mild to severe diarrhoea to, more unusually, severe inflammation of the bowel (known as pseudomembranous colitis). People who have been treated with broad spectrum antibiotics, people with serious underlying illnesses, and older people are at greatest risk – more than 80% of CDIs reported are in people aged over 65 years.

In the quarter up to December 2011 there were 4345 reports of CDI\(^2\), equivalent to 34 per 100,000 population in England. A recent systematic review found that in Europe the incremental cost of CDI ranged from £4577 to £8843 driven primarily by increased length of hospital stay\(^3\). According to a Department of Health impact assessment report in 2010, the best estimate of costs to the NHS associated with a CDI is around £10,000\(^4\).

Mild cases of CDI associated with treatment with broad spectrum antibiotics may recover after stopping the causative antibiotic therapy, although this approach is not straightforward in clinical practice given the concern that symptoms may worsen. Conservative treatment often is not sufficient for moderate to more severe cases and targeted antibiotic therapy is required, most
commonly with oral metronidazole or vancomycin. Both drugs are, in most cases, effective in treating CDI, but about a quarter of patients who initially respond to these agents have a clinical recurrence.


Product overview

Drug action

Fidaxomicin (Dificlir) is the first in a new class of macrocyclic antibiotics and has recently been licensed by the European Medicines Agency[5] (EMA). It has a narrow spectrum of antibacterial activity mainly directed against C difficile and exerts moderate activity against some other Gram-positive species. It is very poorly absorbed systemically and exerts its activity in the gastrointestinal tract.

Licensed therapeutic indications

Fidaxomicin is indicated[6] in adults for the treatment of CDI, also known as C difficile-associated diarrhoea. Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

Course and cost

The recommended dose for fidaxomicin is one 200 mg tablet twice daily for 10 days, with or without food. The product has been launched at a cost of £1350 (excluding VAT) for a 10-day course[7].
Evidence review

This evidence review is based on two, multi-centred, randomised, double-blind trials with almost identical designs and essentially similar results (see table 1). Allocation was concealed in both studies. These trials assessed the non-inferiority of fidaxomicin (200 mg twice daily) with vancomycin (125 mg four times daily) for 10 days in patients aged 16 years or older with mild to severe CDI. Mild to severe CDI was defined as more than three bowel movements in the 24 hours before randomisation and the presence of either *C difficile* toxin (A or B).

One study (Louie et al.) included patients in North America only. The other (Cornely et al.) included patients in Europe (approximately 40% of total) as well as North America. In the Cornely et al. study 54% of patients were 65 years or older, as were 46% of patients in the Louie et al. study.

Table 1 Summary of the studies

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Fidaxomicin</th>
<th>Vancomycin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study 1: Louie et al. (Study in USA and Canada)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified ITT group</td>
<td>n = 287</td>
<td>n = 309</td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>88.2%</td>
<td>85.8%</td>
<td>Lower boundary of 97.5% CI for difference = −3.1%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>15.4%</td>
<td>25.3%</td>
<td>Difference 9.9% (95% CI 2.9 to 16.6%; p = 0.005)</td>
</tr>
<tr>
<td>Sustained response</td>
<td>74.6%</td>
<td>64.1%</td>
<td>Difference 10.5% (95% CI 3.1 to 17.7%; p = 0.006)</td>
</tr>
<tr>
<td>Per protocol group</td>
<td>n = 265</td>
<td>n = 283</td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>92.1%</td>
<td>89.8%</td>
<td>Lower boundary of 97.5% CI for difference = −2.6%</td>
</tr>
<tr>
<td></td>
<td>Study Group 1</td>
<td>Study Group 2</td>
<td>Difference (95% CI)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>13.3%</td>
<td>24.0%</td>
<td>10.7% (3.3% to 17.9%); p = 0.004</td>
</tr>
<tr>
<td><strong>Sustained response</strong></td>
<td>77.7%</td>
<td>67.1%</td>
<td>10.6% (3.1% to 17.9%); p = 0.006</td>
</tr>
<tr>
<td><strong>Safety group</strong></td>
<td>n = 300</td>
<td>n = 323</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>62.3%</td>
<td>60.4%</td>
<td></td>
</tr>
<tr>
<td>Any adverse event related to study drug</td>
<td>9.7%</td>
<td>9.0%</td>
<td></td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>25.0%</td>
<td>24.1%</td>
<td></td>
</tr>
</tbody>
</table>

**Study 2: Cornely et al. (Study in USA, Canada and Europe)**

<table>
<thead>
<tr>
<th></th>
<th>Study Group 1</th>
<th>Study Group 2</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical cure</strong></td>
<td>87.7%</td>
<td>86.8%</td>
<td>-4.9%</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>12.7%</td>
<td>26.9%</td>
<td>14.2% (6.8% to 21.4%); p = 0.0002</td>
</tr>
<tr>
<td><strong>Sustained response</strong></td>
<td>76.6%</td>
<td>63.4%</td>
<td>13.2% (5.2% to 20.9%); p = 0.001</td>
</tr>
<tr>
<td><strong>Per protocol group</strong></td>
<td>n = 216</td>
<td>n = 235</td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>91.7%</td>
<td>90.6%</td>
<td>-4.3%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>12.8%</td>
<td>25.3%</td>
<td>12.5% (4.4% to 20.3%); p = 0.002</td>
</tr>
<tr>
<td>Sustained response</td>
<td>79.6%</td>
<td>65.5%</td>
<td>14.1% (5.9% to 22.1%); p = 0.0008</td>
</tr>
<tr>
<td><strong>Safety group</strong></td>
<td>n = 264</td>
<td>n = 260</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>75%</td>
<td>71.5%</td>
<td></td>
</tr>
<tr>
<td>Any adverse event related to study drug</td>
<td>11.7%</td>
<td>13.8%</td>
<td></td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>26.5%</td>
<td>22.3%</td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients.

1. Met inclusion criteria and received at least one dose of study drug. A number of patients were excluded after randomisation as they failed to meet the inclusion criteria.
2. Resolution of diarrhoea and no need for further treatment.
3. Reappearance of diarrhoea within 4 weeks/30 days after cessation of treatment, a positive *C difficile* test and need for more treatment.
4. Resolution of diarrhoea without recurrence.
5. Met modified ITT criteria and additionally took at least 3 days of study drug for failures or 8 days for cures, had no major protocol violations and had an end of therapy assessment for cure.
6. Included all patients who received at least one dose of study drug and underwent at least one safety assessment.

**Clinical effectiveness**

The primary endpoint in both studies was clinical cure, defined as resolution of diarrhoea and no further need for treatment. The proportion of patients who were cured but subsequently had recurrence during a 4-week or 30-day follow-up was also investigated, as was the total proportion of patients who did not have a recurrence during the follow up period (termed sustained response or global cure). Both were secondary outcomes. Non-inferiority was pre-specified for the primary end-point with a margin of 10%.

In both studies fidaxomicin was found to be non-inferior to vancomycin with regard to clinical cure. However, recurrence rates were significantly lower and sustained response significantly higher in the fidaxomicin groups, based on modified intention-to-treat (ITT) and per protocol (PP) analysis. Key results are shown in table 1.

A reduced risk of recurrence was not observed in the subgroup of patients with the virulent ribotype 027 strain of *C difficile*. Within the Cornely et al. study, the ribotype 027 strain accounted for 10% of patients in Europe and 46% of patients in the USA and Canada.

A post hoc analysis found that in the absence of concomitant antibiotic use during the treatment phase, clinical cure rates for fidaxomicin and vancomycin were similar. However fidaxomicin was significantly more effective than vancomycin in achieving clinical cure in the presence of concomitant antibiotic therapy.  

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Safety

Side-effect profiles were similar between studies. There were no significant differences between vancomycin and fidaxomicin with regard to the number of adverse events (total or related to treatment) (see table 1). Serious adverse events including deaths were reported in both studies; however, these appear to be consistent with the clinical condition of individual patients and were reported at a similar rate in the two treatment arms in both studies.

Adverse events possibly or definitely related to the study treatment were primarily gastrointestinal (nausea, vomiting, diarrhoea, and abdominal pain).

Evidence strength and limitations

The study design and analysis of results was appropriate to demonstrate non-inferiority of fidaxomicin to vancomycin in patients with CDI of varying severities.

Caution is required when translating the results of these studies to routine clinical practice in accordance with HPA guidance[9], which recommends different treatments according to severity. Many patients included in the study had mild to moderate CDI (approximately 60%). For these patients, HPA guidance recommends initial treatment with metronidazole and not vancomycin. No clinical trials have compared the efficacy or safety of fidaxomicin with metronidazole. Of the approximately 40% of patients who were classified as having severe CDI, vancomycin would be an appropriate first-line treatment.

There is limited experience of using fidaxomicin in seriously ill patients, with only eight patients in the combined licensing studies diagnosed with pseudomembranous colitis. Experience is also limited in patients with severe comorbidities (for example, renal or hepatic impairment, inflammatory bowel disease). In such patients there is a possibility of greater systemic absorption. Caution is needed in these patients when using fidaxomicin in view of the uncertain benefits and risks.

As discussed earlier, only one study included European participants, and the prevalence of different C difficile strains differed between the two studies. For example, the more virulent ribotype 027 strain was more prevalent in North America than in Europe. Although overall results for both trials were essentially the same, because a high proportion of the strains from European patients were not identified, it was not possible to associate the outcome of results with strain.
Context

Treatment alternatives

See HPA guidance\(^{[10]}\) for full details of the currently recommended treatments for CDI. If antibacterial treatment is necessary, HPA guidance currently recommends the following first-line treatments:

- metronidazole 400–500 mg three times daily for 10 to 14 days for mild and moderate CDI
- vancomycin 125 mg four times daily for 10 to 14 days for severe CDI.

For first recurrence of infection, the same antibiotic used to treat the initial episode should be repeated (unless the first episode was treated with metronidazole and the recurrence is severe CDI, in which case vancomycin should be used).

Costs of treatment alternatives

The cost of 10 days' treatment with oral metronidazole (400 mg three times daily) is £2.53, and the cost of 10 days' treatment with oral vancomycin (125 mg four times daily) is £188.27 (Drug Tariff, June 2012)\(^{[11]}\).

Estimated impact for the NHS

Likely place in therapy

The role of fidaxomicin will be reviewed by HPA, and the HPA guidance\(^{[11]}\) updated in due course. In the meantime, when considering the use of fidaxomicin, the potential benefits should be considered
alongside the medical need, the risks of treatment and its relatively high cost in comparison with other treatments. These studies suggest an advantage of fidaxomicin over vancomycin in preventing recurrence of CDI and, subject to satisfactory economic analysis, fidaxomicin might have a useful role in treating patients who have a recurrence of CDI or who are at high risk of recurrence.

According to the commentary\textsuperscript{[a]} accompanying the article by Cornely and colleagues, for every 10 patients treated with infection, about 9 usually respond to treatment. However, 2 or 3 of these will have recurrent symptoms, primarily in the first month after treatment. At present, it is difficult to predict the likelihood of recurrent infections and justify the high cost of fidaxomicin in the absence of a prospective, simple but accurate scoring system, or laboratory test, to help clinicians to make informed treatment choices.

Concomitant antibiotics are an important risk factor in the management of CDI, because they are associated with reduced chance of clinical cure, increased recurrence risk, and extended time to resolution of diarrhoea. Therefore, in patients with CDI who need to continue other antibiotics, their risk of CDI recurrence is greater. Fidaxomicin could be considered in such cases\textsuperscript{[a]}.

Further studies are necessary to establish the safety and efficacy of fidaxomicin for repeated use. The drug should be used cautiously in patients with severe renal impairment, moderate to severe hepatic impairment, inflammatory bowel disease, pseudomembranous colitis or fulminant or life threatening CDI. See the summary of product characteristics\textsuperscript{[a]} for further details.

Whether or not strains of \textit{C difficile} susceptible to fidaxomicin can develop resistance is not yet known. A scheme for post-marketing surveillance is underway to monitor changes in resistance patterns of isolated strains of fidaxomicin.

\textit{Estimated usage}

It is not possible to provide estimated usage based on the available data.

\textsuperscript{[a]} Health Protection Agency (2009) \textit{Clostridium difficile: how to deal with the problem}

\textsuperscript{[a]} Wilcox MH (2012) \textit{Progress with a difficult infection. The Lancet Infectious Diseases} 12 256–7

\textsuperscript{[a]} Astellas Pharma Ltd (2012) \textit{Dificlir (fidaxomicin) product information. Summary of Product Characteristics}
About this evidence summary

This document provides a summary of the published evidence. The strengths and weaknesses of the relevant evidence are critically reviewed, but this summary is not NICE guidance.

For information about the process used to develop this evidence summary, see the evidence summaries: new medicines – interim process statement.

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