

June 2012

FIDAXOMICIN (*DIFICLIR*TM)

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Summary

The drug and the review

- Fidaxomicin is a novel antibiotic. It is given orally at a dose of 200mg twice a day for 10 days for the treatment of *Clostridium difficile* (*C. difficile*) infection.
- Fidaxomicin is a narrow spectrum macrocyclic, bactericidal, antibacterial agent. It exerts its action by inhibiting RNA synthesis by bacterial RNA polymerase. The aim of this review is to evaluate the evidence to support the use of fidaxomicin for the treatment of *C. difficile* infections.

Background

- *C. difficile* is a bacterium that can cause diarrhoea and lead to colitis, other serious intestinal conditions and in severe cases, death.
- Between April 2010 and March 2011 there were a total of 21,695 reported cases of *C. difficile* occurring in NHS acute trusts in England in patients over 2 years old, of which 16,869 of these were in patients over 65 years of age.
- Fidaxomicin was approved in the EU in December 2011 for the treatment of *C. difficile* infections (CDI) also known as *C. difficile* associated diarrhoea. It is also licensed and available in the USA.

Literature

- Searches were carried out on Medline, Embase and IDIS databases. These were supplemented by information supplied by Astellas Pharma, the FDA and the European Medicines Agency.
- 1 open label dose-ranging phase 2A study and 2 large randomised active controlled phase 3 trials vs. vancomycin were identified.

Efficacy Studies

The efficacy and safety of fidaxomicin has been studied in one published open label, dose ranging phase 2A trial (N=356) and 2 prospective, multi-centre, phase 3, randomised active controlled trials (N=629 and N=535).

Active comparator studies

The two large phase 3 active comparator trials studied the safety and efficacy of fidaxomicin vs. vancomycin. Both trials used a non-inferiority design. Both trials 003, (N=629) and 004, (N=535) have been published.

Study 003 was analysed both by modified intention-to-treat analysis (mITT), N=596, where at least one dose of study medication was given, and by per-protocol-analysis (N=548). The clinical cure rate with fidaxomicin was non-inferior to vancomycin in both the mITT and the per-protocol groups. The overall rate of recurrence was significantly lower with fidaxomicin (15.4% vs. 25.3%) than with vancomycin, however the rate of recurrence with the NAP1/BI/027 strain of *C. difficile* was the same for fidaxomicin and vancomycin.

The results of study 004 echoed the 003 study and non-inferiority to vancomycin was demonstrated. Fidaxomicin treated patients had a similarly lower rate of recurrence of *C. difficile* infection than vancomycin treated patients in the mITT population; 12.7% vs. 26.9% with fidaxomicin and vancomycin respectively. The prevalence of the *C. difficile* strains differed between the 2 studies. In the North American trial (003) the 027 strain was more common than was found to be the case in the 004 study which included European patients.

No long-term follow up studies were identified although studies in paediatrics, surveillance studies and a study looking at use in patients with recurrence of *C. difficile* infection are planned.

Safety

The safety profile of fidaxomicin appears to be similar to oral vancomycin. Side effects reported in the clinical trials include nausea and vomiting, hyperkalaemia, headache and abdominal cramps.

Critical evaluation

In both the North American trial (003) and the trial including European and North American patients (004); fidaxomicin was administered for 10 days. Both trials were designed to show non-inferiority to vancomycin at 10 days and this was demonstrated in both trials.

Data from both trials appeared to show a significant difference in the recurrence rates of *C. difficile* infection between the fidaxomicin and the vancomycin groups. Recurrence rates in the fidaxomicin treatment group for the mITT population in studies 003 and 004 were 15.4% and 12.7% respectively, compared with 25.3% and 26.9% respectively, for vancomycin. Looking at the subset of European specific data from the 004 trial, recurrence rates were 23% for vancomycin vs. 9% for fidaxomicin ($p=0.011$) in European patients.

The NNT to prevent recurrence of infection in 1 patient within 4 weeks of treatment was 6.94 in study 003 and 10.6 in study 004. This gave an average overall NNT of 8.53.

The authors of both studies were keen to emphasise the superiority of fidaxomicin vs. vancomycin in reducing recurrence and sustained cure of *C. difficile*. In study 003 sustained cure was an exploratory endpoint only. In study 004 this was changed to a secondary efficacy endpoint.

Clinical recurrence was evaluated as a pre-defined secondary efficacy endpoint in patients who had a follow up assessment between days 36 and 40 after randomisation. Data from the 003 study suggested that when all strains of *C. difficile* were included, fidaxomicin showed superiority to vancomycin at the secondary end-point of recurrence. However, it was not superior to vancomycin relapse rates with respect to the NAP1/BI/027 (BI) strain which is more difficult to treat.

When the data from the 004 study, which included European patients, was taken into account and the outcomes in fidaxomicin and vancomycin- treated patients were compared, there were no significant differences in clinical cure rates among patients with infections due to ribotype 027. There was also no significant difference in recurrence rates between vancomycin and fidaxomicin in respect of infections due to the 027 strain.

Concomitant antibiotics were prescribed for 275 patients (27.5% of total). In the absence of concomitant antibiotic use during the 10 days treatment phase, clinical cure rates for fidaxomicin and vancomycin were similar (92.3% vs. 92.8%; $p=0.80$). However, when patients received one or more antibiotics concurrently, clinical cure rates were 90.0% vs. 79.4% ($p=0.04$), respectively. The global or sustained cure rate was 80.8% and 69.1% ($p<0.001$) when patients received no additional antibiotics at any time during the study period, and 72.7% vs. 59.4% ($p=0.02$) when they did. Recurrence rates were 16.9% vs. 29.2% ($p=0.048$) when patients received other antibiotics.

Potential benefits over existing technologies

- Fidaxomicin is administered less frequently than existing treatments.
- Unlike metronidazole, fidaxomicin is minimally absorbed from the GI tract. This may have an advantage in terms of systemic adverse effects.
- Fidaxomicin may be more effective than vancomycin at reducing recurrence of *C. difficile* infection in those patients with the more common strains of *C. difficile*.
- Fidaxomicin is a bactericidal antimicrobial agent. This ability to kill clostridium bacteria, rather than merely prevent them from reproducing, may offer a theoretical advantage in terms of drug resistance. The use of vancomycin (which is bacteriostatic) has been associated with the emergence of vancomycin-resistant strains of bacteria.
- No resistant strains have been observed with fidaxomicin. According to the SPC "there are no known transferable elements that confer resistance to fidaxomicin. Also no cross-resistance has been discovered with any other antibiotic class including beta-lactams, macrolides, metronidazole, quinolones, rifampicin and vancomycin. Specific mutations of RNA polymerase are associated with reduced susceptibility to fidaxomicin."

Potential disadvantages over existing technologies

- A course of fidaxomicin is 8 times more expensive than vancomycin and significantly more expensive than metronidazole.
- There were a number of exclusion criteria in the phase 3 trials. As a result the safety and efficacy of fidaxomicin in these patient groups is not known.
- Fidaxomicin should be used in caution in patients with severe renal failure, moderate to severe hepatic impairment, pseudomembranous colitis, fulminant or life-threatening *C. difficile*, and in patients with inflammatory bowel disease.

Health Economics

The cost of *Dificlir* will be £135 per day, making the cost of a 10 day course £1,350 compared to £5-13 per day for oral vancomycin.

Estimated cost per 100 cases of CDI (provided by Astellas)

Budgetary impact data for fidaxomicin has been provided by the company based on treating 100 cases of CDI. Two models are outlined below: using fidaxomicin first line in all CDI patients and using fidaxomicin in recurrent CDI patients only.

Treating 100 patients with CDI with fidaxomicin first line instead of metronidazole and vancomycin and also any recurrences of CDI, would result in 111 patients being treated (this compares to 137 cases as would be expected with current antibiotics). The net budget impact of this is £8,131.

If fidaxomicin is only used to treat recurrences of CDI in 100 patients treated initially with metronidazole and vancomycin, the net budget impact is £15,886. The increase in costs is due to more patients experiencing recurrences with metronidazole and vancomycin than with fidaxomicin.

Astellas have stated that it is logical to implement fidaxomicin earlier within the treatment protocol to derive the maximum cost effectiveness and impact on overall CDI cases, rather than only implementing fidaxomicin after a patient has already experienced a recurrent episode.

This budget impact modelling does not account for overall improvements in infection control, and avoidance of penalties or fines.

Issues for consideration

- Fidaxomicin has shown non-inferiority to vancomycin for the treatment of *C. difficile* with less frequent dosing. As most patients will be treated in hospital this may not be a major benefit.
- Unlike metronidazole, fidaxomicin is minimally absorbed from the gastro-intestinal tract; however, as there have been no head to head phase 3 studies vs. metronidazole, the clinical significance of this is unclear. Previous studies showed that metronidazole is as effective as vancomycin for treating non-severe disease and inferior to vancomycin for severe disease.
- Fidaxomicin has a comparable safety profile to oral vancomycin.
- In both phase 3 studies the recurrence rate was significantly lower in the fidaxomicin groups compared to the vancomycin groups.
- Fidaxomicin did not reduce recurrence rates in all strains of *C. difficile*, and some strains were more frequent, hence driving the result. Fidaxomicin was no better at reducing recurrences of *C. difficile* infection in the patients infected with the 027 strain. It should be noted, however, that the actual rates of ribotype 027 (34% across both trials) were considerably higher than the current rates in the UK (2-5%).
- The prevalence and severity of infection caused by the different strains of *C. difficile* varies between countries and over time. Current trends indicate a significant decline in ribotype 027 in the UK, with levels at approximately 2-5%. Depending on what happens with prevalence rates of this and other strains in the future; the overall impact of fidaxomicin may be affected.
- Clinicians currently do not routinely know which strain of *C. difficile* is causing the infection at the start of therapy. Also identifying individuals at the greatest risk of recurrence is not straightforward. If the cost of fidaxomicin leads to a high degree of patient selection then these patients have not been sufficiently studied in the clinical trials to date.
- Fidaxomicin has demonstrated potent *in-vitro* activity against *C. difficile* with limited or no activity against normal faecal flora.
- Fidaxomicin has shown *in-vitro* activity against non *C. difficile* Gram positive anaerobes including vancomycin resistant enterococci. In theory therefore, fidaxomicin may reduce the risk of colonization of the gut by resistant strains of Gram positive anaerobes. This appears to have been the case in the clinical trials and may influence drug choice in some cases/localities where resistant strains are a problem.
- Fidaxomicin has demonstrated the ability to inhibit spore and toxin production *in-vitro*. The clinical significance of this has not been considered in the published trials.

Background

Fidaxomicin (*Dificlir*TM) is a first in class, narrow spectrum, macrocyclic, antibacterial agent for oral use. It is intended for the treatment of *Clostridium difficile* (*C. difficile*) infection and exhibits excellent activity against *C. difficile*. (1)

Fidaxomicin is bactericidal and exerts its action by inhibiting RNA synthesis by bacterial RNA polymerase. It interferes with RNA polymerase at a distinct site from that of rifamycins. Inhibition of the Clostridial RNA polymerase occurs at a concentration 20-fold lower than that for the *E.coli* enzyme (1 µM vs. 20 µM); partly explaining the specificity of fidaxomicin activity. Fidaxomicin has been shown to inhibit *C. difficile* sporulation in vitro. (2)

A marketing authorisation for fidaxomicin tablets for the treatment of *Clostridium difficile* infections (CDI) was granted in the EU in December 2011. (2)

Fidaxomicin was developed by the US company - Optimer and approved in the US in 2011, under the trade name *Dificid*, for the treatment of *Clostridium difficile*-associated diarrhoea (CDAD). (3) Astellas Pharma in the UK holds the marketing authorisation and will be responsible for the European commercialisation and development of the product.

Fidaxomicin, which has completed two large randomised phase 3, double blind, controlled, multi-centre studies, has shown:

- non-inferiority to vancomycin in the primary efficacy variable, clinical cure at end of therapy, and superiority in the secondary endpoints of recurrence rate and global cure rate within 36 to 40 days after initiation of treatment. (2,4,5,6)
- a comparable safety profile to oral vancomycin. (2,5,6)
- that fewer individuals developed intestinal colonization with vancomycin-resistant enterococci (VRE) among the fidaxomicin-treated group through addi-

tional faecal flora analysis in the trials. (4,5)

Patients' at the greatest risk of recurrence may benefit the most from treatment with fidaxomicin, however identifying this groups of patients is currently not straight forward. (7) This may change over time.

Fidaxomicin is not currently in the NICE programme. (8)

C. difficile is a Gram-positive anaerobic spore forming bacterium that can cause diarrhoea and lead to colitis, other serious intestinal conditions, and death in severe cases. (1,9) *C. difficile* bacteria are found in the stool of an infected person, and others can become infected if they touch items or surfaces contaminated with bacteria or spores and then touch their mouths. (6) *C. difficile* is responsible for 15-25% of all antibiotic-associated diarrhoea. (1)

Clostridium difficile infection (CDI) has become an increasingly important healthcare-associated complication in many countries. (5) The incidence and severity of *C. difficile* infection, which usually occurs after exposure to broad spectrum antibiotics, had been increasing until about 4 or 5 years ago and in some countries was linked to the emergence of a hyper-virulent *C. difficile* strain known as North American Pulsed Field type 1 (NAP1), or restriction-endo-nuclease analysis (REA) type BI, or polymerase-chain-reaction ribotype 027. These are referred to collectively as NAP1/BI/027. (4)

Fidaxomicin has demonstrated potent in-vitro activity against *C. difficile* with limited or no activity against normal faecal flora. It is minimally absorbed from the intestinal tract, even in the presence of intestinal inflammation. (6)

Current treatment options

C. difficile infection is a serious diarrhoeal illness associated with substantial morbidity and mortality. Patients generally have a Response to oral vancomycin or

Table 1 - Current treatment options for *C. difficile*

| European Society Clinical Microbiology and Infectious Diseases definition of <i>C. difficile</i> infection | Treatment |
|---|--|
| Non-severe Stool frequency < 4 times daily; no signs of severe colitis | If clearly induced by the use of antibiotics, the infection may be treated by stopping the inducing antibiotic. Observe patients closely for any signs of clinical deterioration and place on therapy immediately if this occurs Oral metronidazole 400-500mg three times a day for 10 – 14 days. |
| Severe An episode of CDI with one or more signs of severe colitis. CDI without signs of severe colitis in patients with advanced age (≥65), serious co-morbidity, ICU admission, or immunodeficiency may be regarded as severe. | Oral vancomycin 125mg four times a day for 10 – 14 days, or if unresponsive, high dose oral vancomycin (up to 500mg four times a day) +/- intravenous metronidazole 500mg three times a day, with addition of oral rifampicin (300mg twice a day) or IV immunoglobulin (400mg per kg). |
| Life threatening | Oral vancomycin up to 500mg four times a day for 10 – 14 days via a nasogastric tube or rectally plus intravenous metronidazole 500mg three times a day. |
| Recurrent | For the first recurrence, the same antibiotic used to treat the initial episode, is repeated. Vancomycin 125mg four times a day is recommended for subsequent episodes. |

metronidazole; and these are considered the agents of choice however, the rate of recurrence is high. (4,10) *C. difficile* is treated according to severity. Table 1 shows the current recommended UK HPA treatment guidelines for *C. difficile*. (11)

Alternative non-traditional approaches

In the years preceding the trials, increasing frequency of infection and hypervirulent *C. difficile* strains resulted in more severe disease as well as therapeutic failures with traditional treatments (metronidazole and vancomycin). Studies assessing non-traditional therapies for the prevention and treatment of primary or

recurrent *C. difficile* infection were reviewed by Venuto et al in 2010. A literature search (MEDLINE 1984-2010) was conducted, and of the 98 studies identified, 21 met the inclusion criteria. Five clinical trials and one retrospective medical record review evaluated probiotic or prebiotic formulations for the prevention of *C. difficile* infection. Only one of these studies, which included *Lactobacillus casei* and *L. bulgaricus* in the probiotic formulation, showed efficacy. Ten clinical trials evaluated treatment of an initial episode of *C. difficile* infection (primary treatment) with the antimicrobials fidaxomicin, fusidic acid, rifampicin, teicoplanin, and nitazoxanide, as well as the toxin-binding polymer, tolevamer.

Only nitazoxanide and teicoplanin demonstrated non-inferiority when compared with vancomycin or metronidazole. Four prospective studies and one retrospective study evaluated treatment of relapsing *C. difficile* infection. Probiotic formulations for the prevention and treatment of recurrent *C. difficile* infection have not proved to be clinically warranted. (10) Venuto et al concluded- nitazoxanide, teicoplanin, and fidaxomicin may be considered as alternatives to traditional treatment; however, clinical experience was at that time limited with these agents for this indication. Bacteriotherapy with faecal instillation has demonstrated high clinical cure rates in case studies and in a retrospective study; however, randomised clinical trials are lacking for this therapeutic approach. (10)

Data have shown that the rate of recurrence of *C. difficile* infection is increased in patients in whom anti-*C. difficile* toxin A IgG antibodies do not develop. Immunological approaches to the prevention and treatment of recurrences are therefore in development and include the

use of immunoglobulins, monoclonal anti-*C. difficile* toxin antibodies and active immunisation. (9)

Gerding and Johnson, writing in *Clinical Infectious Diseases* in 2011 (10), collated reports of current treatments in development for *C. difficile* as well as existing antimicrobial and non-antimicrobial therapeutic options. Table 2 lists some of the management approaches considered in the treatment of *C. difficile* infection. (12)

Fidaxomicin dose

The recommended dose of fidaxomicin in adults and the elderly (≥ 65 years of age) is one 200mg tablet orally twice a day for 10 days with or without food. (2)

Special Populations

Pregnancy - Reproduction studies in animals revealed no evidence of harm to the foetus due to fidaxomicin. As a precautionary measure, it is preferable to avoid the use of fidaxomicin during pregnancy. (2)

Table 2 – Management of *C. difficile* infection

| | |
|---|--|
| Current available antimicrobial agents | Vancomycin Metronidazole Rifaximin Nitazoxanide Tigecycline Bacitracin Teicoplanin Fusidic acid Fidaxomicin (Q2 2012) |
| Antimicrobial agents in clinical development | Ramoplanin (nanotherapeutics) CB-183,315 (Cubist) |
| Currently available non-antimicrobial agents | Intraluminal toxin neutralising agents Intravenous immunoglobulin |
| Non-antimicrobial agents in clinical development | Intraluminal toxin neutralising agents Bovine whey protein Non-toxigenic <i>C. difficile</i> Monoclonal antibodies Active vaccines |
| Procedures | Faecal transplants |

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Breast feeding - It is not known whether fidaxomicin or its metabolites are excreted in human milk. Although no effects on the breastfed newborns/infants are anticipated since the systemic exposure to fidaxomicin is low, a risk to newborns cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from fidaxomicin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. (2)

Paediatric use

Safety and efficacy of fidaxomicin has not been established in patients <18 years of age. (2)

Renal and hepatic impairment

Studies have shown that no dosage adjustments are considered necessary based on renal impairment. The metabolism and excretion of fidaxomicin is not expected to be significantly affected by hepatic impairment although the impact on the pharmacokinetics of fidaxomicin in this group of patients has not been evaluated. (2)

Special warnings and precautions for use

Due to limited clinical data, fidaxomicin should be used with caution in patients with severe renal impairment, moderate to severe hepatic impairment, pseudomembranous colitis and fulminant or life threatening *C. difficile* infection. (2)

There are no data in patients with concomitant inflammatory bowel disease. Fidaxomicin should be used with caution in these patients due to the risk of enhanced systemic absorption and potential risk of systemic adverse reactions. (2)

Co-administration of potent P-gp inhibitors such as ciclosporin, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone is not recommended, see drug/food interactions. (2)

Drug / Food Interactions

Fidaxomicin is a substrate of P-gp and may be a mild to moderate inhibitor of intestinal P-gp. (2)

In-vivo studies were conducted to evaluate intestinal drug-drug interactions of fidaxomicin as a P-gp substrate, P-gp inhibitor, and inhibitor of major CYP enzymes expressed in the gastrointestinal tract (CYP3A4, CYP2CP, and CYP2C19). (3) Fidaxomicin and its main metabolite, OP-1118, are substrates of the efflux transporter, P-gp, which is expressed in the gastrointestinal tract. (3)

Co-administration of single doses of the P-gp inhibitor ciclosporin A and fidaxomicin in healthy volunteers, resulted in a 4- and 2- fold increase in fidaxomicin C_{max} and AUC, respectively and in a 9.5 and 4-fold increase in C_{max} and AUC, respectively, of the main active metabolite OP-1118. As the clinical relevance of this is unclear, co-administration of potent P-gp inhibitors such as ciclosporin, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone is not recommended. (2)

Fidaxomicin (200mg twice daily) had a small but not clinically relevant effect on digoxin exposure. However, a larger effect on P-gp substrates with lower bioavailability more sensitive to intestinal P-gp inhibition such as dabigatran etexilate cannot be excluded. (2)

Safety

The safety of fidaxomicin 200mg twice daily for 10 days was evaluated in 564 patients in the active comparator controlled trials, of which 86.7% received the full course of treatment. Thirty-three (5.9%) patients withdrew from the trials as a result of adverse reactions. The primary adverse reaction leading to discontinuation was vomiting, which occurred with an incidence of 0.5% in both fidaxomicin and vancomycin patients in the phase 3 studies. (2,3)

Table 3 - Selected adverse reactions with an incidence of $\geq 2\%$ reported in fidaxomicin and vancomycin treated patients in the two active controlled trials. (3)

| | Fidaxomicin (N=564) | Vancomycin (N=583) |
|-------------------------------------|----------------------------|---------------------------|
| Anaemia | 14 (2%) | 12 (2%) |
| Neutropenia | 14 (2%) | 6 (1%) |
| Nausea | 62 (11%) | 66 (11%) |
| Vomiting | 41 (7%) | 37 (6%) |
| Abdominal Pain | 33 (6%) | 23 (4%) |
| Gastrointestinal Haemorrhage | 20 (4%) | 12 (2%) |

The most common treatment related adverse reactions were nausea (2.7%), vomiting (1.2%) and constipation (1.2%). (2)

The adverse-event profile was similar for the fidaxomicin and vancomycin groups and is shown in table 3.

The following reactions were reported in $<2\%$ of patients taking fidaxomicin in controlled trials:

Gastrointestinal disorders: abdominal distension, abdominal tenderness, dyspepsia, dysphagia, flatulence, intestinal obstruction, megacolon.

Investigations: increased blood alkaline phosphatase, decreased blood bicarbonate, increased hepatic enzymes, and decreased platelet count.

Metabolism and nutrition disorders: hyperglycaemia, metabolic acidosis.

Skin and Subcutaneous Tissue disorders: drug eruption, pruritus, rash.

Clinical Studies

Phase 3 trials followed a dose-finding, randomised, open-label phase 2 trial where fidaxomicin was associated with a good clinical response and a low rate of recurrence. (13)

In the two randomised, double-blinded trials, a non-inferiority design was used to demonstrate the efficacy of fidaxomicin (200mg twice daily for 10 days) compared

to vancomycin (125mg four times daily for 10 days) in adults with CDAD. (2,3) The rate of recurrence in the 30 days following treatment was assessed as a secondary endpoint. The rate of recurrence (including relapses) was significantly lower with fidaxomicin (14.1% vs. 26.0% with a 95% CI of [-16.8%, -6.8%]), however these trials were not prospectively designed to prove prevention of re-infection with a new strain. (2)

Table 4 shows the key inclusion and exclusion criteria for these trials.

Patient demographics and baseline disease were similar in the two trials. Patients had a median age of 64 years, were mainly white (90%), female (58%), and inpatients (63%). The median number of bowel movements per day was 6 and 37% of subjects had severe CDAD (defined as 10 or more unformed bowel movements a day or WBC $\geq 15,000/\text{mm}^3$). Diarrhoea alone was reported in 45% of patients and 84% of subjects had no prior CDAD episode. (2,3)

The primary endpoint was the clinical response rate at the end of therapy based on improvement in diarrhoea or other symptoms such that, in the investigators opinion, no further treatment for CDAD was needed. (2,3)

A secondary additional efficacy endpoint was sustained clinical response at 25 days

Table 4 – Key inclusion and exclusion criteria for the two randomised, phase 3, active comparator trials

| Inclusion criteria | Exclusion criteria |
|--|---|
| <ul style="list-style-type: none"> • 16 years of age or over (apart from the German patients in study 004 who were aged over 18 years). • No more than 24 hours pre-treatment with vancomycin or metronidazole. • Presence of <i>C. difficile</i> infection defined by >3 unformed bowel movements (or >200mL of unformed stool for subjects having rectal collection devices) in the 24 hours prior to randomisation <i>and</i> presence of either A or B <i>C. difficile</i> toxin in the stool within 48 hours of randomisation. (NB: study 004 clarified this further, stating “presence of either A or B of <i>C. difficile</i> in the stool within 48 hours of randomisation for metronidazole failures, or within 96 hours of randomisation for subjects with ≤ 24 hours pre-treatment with CDI therapy.”) | <ul style="list-style-type: none"> • >1 prior <i>C. difficile</i> infection episode in the past 3 months • Life threatening/fulminant infections • Hypotension • Septic shock • Peritoneal signs • Significant dehydration • Toxic megacolon • Females who were pregnant or breast feeding • Likely to die within 72 hours from any cause • History of ulcerative colitis or Crohn’s disease |

after the end of treatment. Sustained response was only evaluated in patients who were clinical successes at the end of treatment, and survival without proven or suspected CDAD recurrence 25 days after the end of treatment. (2,3)

The data from both clinical trials was combined for both the EU and USA license applications and both trials have been published. (2,4,5)

The results of the 003 study were published in 2011. (4) It was carried out between May 2006 and August 2008 and enrolled patients from 52 sites in the USA and 15 sites in Canada. Included were 629 adults with acute symptoms of *C. difficile* infection and a positive result for stool toxin test.

Patients were randomised to fidaxomicin (200mg twice daily) or vancomycin (125mg four times daily) orally for 10 days. The primary endpoint was clinical cure (resolution of symptoms and no need

for further therapy as of the second day after the end of the course of therapy).

The secondary endpoints were recurrence of *C. difficile* infection (diarrhoea and a positive result on a stool toxin test within 4 weeks after treatment) and global cure or sustained cure (i.e. cure with no recurrence). For the microbiological evaluation, faecal samples were taken for toxin assays to verify *C. difficile* infection and isolates. Testing occurred at the time of screening or enrolment, at the time of early termination or at the end-of-therapy visit in patients with clinical failure or at visits for the treatment of recurrent infection in patients in whom the disease recurred. (4)

The trial was designed as a non-inferiority study and a one-sided lower 97.5% confidence interval was used in the analysis of the primary end point, the rate of clinical cure, with a non-inferiority margin of -10%. Non-inferiority was demonstrated if the lower boundary of the confidence limit was within the 10% margin. The second-

dary and exploratory endpoints of recurrence and overall cure, which were prospectively defined as descriptive endpoints, were analysed by means of post-hoc hypothesis tests. (4)

548 (87.1%) patients were evaluated for the per-protocol analysis. Rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin in both the modified ITT analysis (88.2% vs. 85.8%) and the per-protocol (PP) analysis (92.1% vs. 89.8%). (4)

Significantly fewer patients in the fidaxomicin group had a recurrence of infection: modified intention-to-treat (ITT) analysis (15.4% vs. 25.3% $p=0.005$), the PP analysis (13.3% vs. 24.0%, $p=0.004$). However, when the strains of *C. difficile* were examined, this showed that the potential advantage with respect to recurrence offered with fidaxomicin, was driven by a reduction in recurrence rates caused by non NAP1/BI/027 strains. For the 35.9% of patients with the NAP1/BI/027 strain, fidaxomicin showed no advantage over vancomycin. (4)

The adverse event profile was similar for the two therapies and there were no significant differences between the fidaxomicin and vancomycin group in the rates of adverse events or serious adverse events. No subjects discontinued the study as a result of intolerance or allergy to the study medicines. The occurrence of any adverse event during the treatment period until 7 days after treatment was reported in 62.3% of the patients in the fidaxomicin group and 60.4% of the patients in the vancomycin group; the occurrence of any serious adverse event was reported in 25.0% and 24.1% of the patients in the two groups, respectively. Adverse events possibly or definitely related to study treatment were mild gastrointestinal and non-specific symptoms. The rates of these events were similar in the two groups (9.7% and 9.0%). There were significantly more serious adverse events related to laboratory finding in the

fidaxomicin group compared with the vancomycin group (4.7% vs. 1.2%, $p=0.01$), this was without an obvious pattern. (4)

In February 2012 Cornely and colleagues published Trial 004. (5) This trial, which included patients from 45 sites in Europe and 41 sites in North America, was conducted between April 2007 and December 2009. The aim of the trial, identical in design and procedures with trial 003, was to compare the efficacy of fidaxomicin and vancomycin in Europe as well as Canada and the USA.

Fidaxomicin demonstrated non-inferiority for clinical cure rate, matching the 003 trial performed in North America only. Fidaxomicin was also associated with a lower rate of recurrence in the 4 weeks after completion of the treatment than vancomycin (15.4% of patients treated with fidaxomicin compared with 25.3% given vancomycin).

There were 524 patients in the safety population and incidences of treatment emergent adverse events were not significantly different between the two groups. Adverse events possibly or definitely related to the study treatment were primarily gastrointestinal symptoms; nausea, vomiting, diarrhoea and abdominal pain, in both groups. 20 of the 264 patients (7.6%) and 17 of the 260 vancomycin patients (6.5%) died.

It was noteworthy that the distribution of *C. difficile* strains in this trial was different from those identified in the 003 trial. The prevalence of the strains identified was consistent with the strains found circulating within Europe at the time the data was collected. Strains isolated in the 004 study were not characterised by PCR ribotyping, however the investigators used an investigation comparing the two methods to align the strain types. The most common strain in Europe was restriction endonuclease analysis group Y (16%), corresponding to ribotypes 020/014. The second most common groups was J, which aligns to ribotype 001 (10%) of isolates. In the European

Clostridium difficile infection study in hospitals in which investigators collected *C. difficile* isolates in November 2008, ribo-type 078 (group BK) was more common than 027 (BI), this differed from this study. Cornely *et al* acknowledged that as such a high number of the strains from Europe were not identified in this trial; some important associations of outcome may have been missed.

Looking at the combined phase 3 trial data for the primary outcome of clinical response (shown in table 5) fidaxomicin is non-inferior to vancomycin based on a 95% confidence interval (CI) the lower limit being greater than the non-inferiority margin of 10%. For the secondary endpoint, the results for sustained clinical response at the end of the follow-up period (also shown in table 5), fidaxomicin was superior to vancomycin. Clinical successes at the end of treatment and mortality rates were similar across treatment arms (approximately 6% in each group). Differences in sustained clinical response were due to lower rates of proven or suspected CDAD during the follow up period in the fidaxomicin patients. (2,3)

Restriction End nuclease Analysis (REA) was used to identify *C. difficile* baseline

isolates in the BI group, isolates were associated with increasing rates and severity of *C. difficile* infection in the years preceding the clinical trials. (2,3) Similar rates of clinical response at the end of treatment and proven or suspected CDAD during the follow-up period were seen in fidaxomicin-treated and vancomycin-treated patients infected with BI isolates. However, fidaxomicin did not demonstrate superiority in sustained clinical response when compared with vancomycin (see Table 6).

In summary, the rates of clinical cure of patients with a single episode of mild to moderately severe non-recurrent *C. difficile* associated-diarrhoea after treatment with fidaxomicin were non-inferior to those after treatment with vancomycin. (2)

Fidaxomicin was associated with a significantly lower rate of recurrence of *C. difficile* infection overall. (2) But looking at the sub-group of the NAP1/BI/027 strain there was no difference in recurrence rates shown between vancomycin and fidaxomicin.

The EPAR concludes: fidaxomicin seems to have the potential to offer a valuable alternative in the treatment of *C. difficile* infection, in particular considering the favour-

Table 5– Clinical response rates at end of therapy and sustained response rates at 25 days post therapy (2,3)

| | Clinical response at end of treatment | | | Sustained Response at Follow-up | | |
|-----------|---------------------------------------|-------------|--------------------------|---------------------------------|-------------|---------------------------|
| | F N (%) | V N (%) | Difference (95% CI) | F N (%) | V N (%) | Difference (95% CI) |
| Trial 003 | 289 (88) | 307 (86) | 2.6% (-2.9%, 8.0%) | 289 (70) | 307 (57) | 12.7% (4.4%, 20.9%) |
| Trial 004 | 253 (88) | 256 (87) | 1.0% (-4.8%, 6.8%) | 253 (72) | 256 (57) | 19.6% (8.7%, 30.0%) |

F=fidaxomicin, V=vancomycin
Confidence interval was derived using Wilson's score method.
Approximately 5%-9% of the data in each trial and treatment arm were missing sustained response information and were inputted using multiple imputation method.

Table 6 - Sustained clinical response at 25 days after treatment by *C. difficile* REA group at baseline

| Initial <i>C. Difficile</i> Group | Fidaxomicin n/N (%) | Vancomycin n/N (%) | Difference (95% CI) * |
|---|---------------------|--------------------|-----------------------|
| Trial 003 | | | |
| BI Isolates | 44/76 (58%) | 52/82 (63%) | -5.5 (-20.3%,9.5%) |
| Non-BI isolates | 105/126 (83%) | 87/131 (66%) | 16.9% (6.3%, 27.0%) |
| Trial 004 | | | |
| BI Isolates | 42/65 (65%) | 31/60 (52%) | 12.9% (-4.2%, 29.2%) |
| Non-BI isolates | 109/131 (83%) | 77/121 (64%) | 19.6% (8.7%, 30.0%) |
| Interaction test between the effect on sustained response rate and BI versus non-BI isolates using logistic regression (p-values): trial 003: 0.0009; trial 004: 0.029). Approximately 25% of the mITT population were missing data for REA group. Confidence intervals were derived using Wilson's score method. | | | |

able effect on relapses and the unique mode of action suggesting a limited potential for promotion of resistance against established antibiotic classes. (2)

A subgroup analysis of patients receiving concomitant systemic antibiotics in the two phase 3 studies of fidaxomicin vs. vancomycin for CDAD was carried out and results published in August 2011. (12) Nine hundred and ninety nine subjects with CDI were treated for 10 days with fidaxomicin or vancomycin, assessed for resolution of symptoms, and followed up for 4 weeks for evidence of recurrence.

Concomitant antibiotics were prescribed for 275 patients (27.5% of total). In the absence of concomitant antibiotic use during the 10 days treatment phase, clinical cure rates for fidaxomicin and vancomycin were similar (92.3% vs. 92.8%; p= 0.80). However, when patients received one or more antibiotics concurrently, clinical cure rates were 90.0% vs. 79.4% (p=0.04), respectively. The global or sustained cure rate was 80.8% and 69.1% (p<0.001) when patients received no additional antibiotics at any time during the study period, and 72.7% vs. 59.4% (p 0.02) when they did. Recurrence rates were 16.9% vs. 29.2% (p=0.048) when patients received other antibiotics. (14)

Health Economics

The cost of *Difficilir* is £135 per day making the cost of a 10 day course £1,350. (15) Comparator drug costs are listed in table 7.

Table 7 - Comparator drug costs

| Drug | ~Cost (16,17) |
|--|-------------------|
| Vancomycin 125mg orally four times a day | £131* for 14 days |
| Metronidazole 400mg orally three times a day | £3 for 14 days |

*most patients will be treated in hospital and therefore vancomycin drug costs will vary. The majority of in-patients will receive the injection orally. With a 1g vial costing around £5 this is less costly than the capsules which cost £131 for 28 x 125mg. (16)

Budget impact

Astellas have provided a budget impact model for fidaxomicin (*Difficilir*TM) in the NHS in England based on a number of assumptions. This model and the assumptions on which it is based are outlined below. (18)

The predominant cost of CDI to the NHS is on prolonged hospital stay. In 1996, a UK

study suggested that CDI was responsible for an additional 21 days of hospital stay per patient, generating an additional per-patient expenditure of £4,107. (18)

Latest figures from the 2010/11 Department of Health Impact Assessment Report for CDI assigns a cost of £10,000 per episode, (18) whilst 5-year incidence data to 2011 suggest readmissions due to CDI recurrence or reinfection involve an additional 12.2 bed days. (18)

Fidaxomicin will be priced at £135 per treatment day, whereas the current standard of care is oral vancomycin at £5–13 per day. Nonetheless, whilst upfront drug investment increases with use of fidaxomicin over oral vancomycin, there is potential a significant decrease in hospitalisation costs due to potentially decreased recurrence admission spells.

Model 1: fidaxomicin first line use in all CDI patients – 100 initial cases

Use of the standard treatment (modelled as 60% metronidazole and 40% oral vancomycin) would be expected to result in a CDI recurrence rate of between 23%

(vancomycin) and 29% (metronidazole) following initial treatment. This would result in 27 patients experiencing a first recurrence. With re-treatment of these 27 first recurrences, using the same agents as previously, 10 patients would be expected to recur for a second time (based on a 40% and 35.5% second recurrence rate for metronidazole and vancomycin, respectively).

Comparatively, only 9 patients would be expected to recur following use of fidaxomicin for all 100 initial cases; this figure would be further reduced to 2 patients following fidaxomicin use at first recurrence (based on a recurrence rate of 9% following treatment of a first CDI episode as observed in the European data within the 004 clinical trial, and 19% following treatment of all first recurrence episodes as observed in the nested subset clinical trial data).

The model presumes per-patient hospital costs of £9,201 for each initial CDI episode, and an additional £5,295 for each recurrence. These values are based on 21 days additional stay for a first episode and 12 days for any recurrent episodes, (18)

DIFICLIR Budget Impact Tool

| Summary | |
|---|---|
| Summary of budget impact modelling introducing DIFICLIR as a first line treatment option for all 100 initial cases, compared to standard metronidazole and oral vancomycin therapy. | |
| Initial infections excl. recurrences | 100 |
| Patient episodes treated with DIFICLIR inc. recurrences | 111 (compared to 137 cases as would be expected with current antibiotics) |
| Incremental drug costs | £146,318 |
| Incremental hospitalisation costs | –£138,188 |
| Net budget impact through use of DIFICLIR in 111 patients | £8,131 |
| Number of CDI cases saved through use of DIFICLIR | 26.1 |
| Percentage reduction in CDI cases through use of DIFICLIR | 19.1% |
| Number of bed days saved through use of DIFICLIR | 318.4 |

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multiplied by a bed day value of approximately £400.

When considering hospitalisation and drug costs only for initial treatment and up to 2 recurrences, fidaxomicin has a net budget impact of £8,131 compared with standard metronidazole/oral vancomycin therapy.

Furthermore, by reducing the number of CDI recurrences vs. oral vancomycin therapy, use of fidaxomicin may also provide additional hospital capacity that would not be otherwise available (e.g., if any surgical beds are occupied by CDI patients). Utilisation of such capacity for other procedures could generate an income for a hospital trust under the Payment by Results system. The potential opportunity of this specific saving may be calculated using the full Astellas fidaxomicin budget impact tool (available separately).

Model 2: DIFICLIR use in recurrent CDI patients only

This scenario investigates fidaxomicin being used for all patients with CDI recur-

rence only (no use in initial CDI episode and 100% use at first and second recurrence). CDI recurrence rates between 23% (vancomycin) and 29% (metronidazole) would still be expected following standard initial treatment (40% receive oral vancomycin, 60% receive metronidazole). Approximately 27 patients would be expected to experience a first recurrence.

With use of fidaxomicin at first recurrence, 5 of these 27 recurrent patients would be expected to present with second recurrence (based on a fidaxomicin recurrence rate of 19.7% following treatment of first recurrence episode), compared with 10 patients if standard oral vancomycin/metronidazole schedules were used (based on a recurrence rate between 35.5% and 40% following treatment of first recurrence episode).

The model presumes per-patient hospital costs of £9,201 for each initial CDI episode, and an additional £5,295 for each recurrence. These values are based on 21 days additional stay for a first episode and

DIFICLIR Budget Impact Tool

| Summary | |
|--|---|
| Summary of budget impact modelling introducing DIFICLIR as the treatment option for any recurrent CDI cases initially treated with standard metronidazole and oral vancomycin therapy. | |
| Initial infections excl. recurrences | 100 |
| Patient episodes treated with DIFICLIR inc. recurrences | 132 (compared to 137 cases as would be expected with current antibiotics) |
| Incremental drug costs | £42,020 |
| Incremental hospitalisation costs | -£26,134 |
| Net budget impact through use of DIFICLIR in 32 patients | £15,886 |
| Number of CDI cases saved through use of DIFICLIR | 4.9 |
| Percentage reduction in CDI cases through use of DIFICLIR | 3.6% |
| Number of bed days saved through use of DIFICLIR | 60.2 |

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12 days for any recurrent episodes, (18) multiplied by a bed day value of approximately £400.

When considering hospital and drug costs only for initial treatment with oral vancomycin/metronidazole and up to 2 recurrences using fidaxomicin only, there is a net budget impact of £15,886 per 100 patients, compared with standard therapy.

This value is £7,755 greater than in Model 1 above, where fidaxomicin was used as a first line agent for all patients.

This is because the significant hospitalisation costs that could potentially be avoided by reducing the number of patients presenting with a first recurrence have not been avoided as fidaxomicin was not the first line treatment choice.

Summary of Budget Impact Modelling

As fidaxomicin offers a significant reduction in recurrence rates compared with oral vancomycin, it is logical to implement fidaxomicin earlier within the treatment protocol to derive the maximum cost effectiveness and impact on overall CDI cases, rather than only implementing fidaxomicin after a patient has already experienced a recurrent episode.

This budget impact modelling does not account for overall improvements in infection control, and avoidance of penalties or fines.

Literature searches

- Searches were carried out on Medline (fidaxomicin.af), Embase (fidaxomicin/) and IDIS (fidaxomicin) databases. These were supplemented by information supplied by Astellas Pharma, the FDA and the European Medicines Agency.
- 3 double-blind, placebo-controlled trials were identified evaluating the efficacy and safety fidaxomicin in the treatment of *C. difficile* infection.

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The London New Drugs Group would like to thank Paul Wade, Consultant Pharmacist, Infectious Diseases, Guys and St Thomas' Hospital and Paul Fieldhouse Principal Pharmacist, Medicines Management, Newcastle University Teaching Hospital, for their comments.

This document reflects the views of the LNDG and may not reflect those of reviewers.