Clinical efficacy of fidaxomicin compared with vancomycin and metronidazole in *Clostridium difficile* infections: a meta-analysis and indirect treatment comparison

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Received 28 January 2014; returned 24 March 2014; revised 12 June 2014; accepted 14 June 2014

Objectives: To evaluate the efficacy of fidaxomicin treatment, which has a limited effect on the normal gut flora, compared with vancomycin and metronidazole treatment in *Clostridium difficile* infections (CDIs).

Methods: A systematic literature review was conducted in July to August 2011 and updated in July 2013. For fidaxomicin versus vancomycin, efficacy was evaluated using meta-analysis of data from two Phase III direct comparative studies (n = 1164). As there were no studies comparing fidaxomicin and metronidazole, an indirect comparison was made using data from three vancomycin versus metronidazole studies (n = 345), using the methodology of Bucher et al. (*J Clin Epidemiol* 1997; 50: 683–91). This provides an OR for the indirect comparison of fidaxomicin versus metronidazole when direct evidence of fidaxomicin versus vancomycin and vancomycin versus metronidazole is available.

Results: Clinical cure rates were similar for fidaxomicin and vancomycin; the OR (95% CI) was 1.17 (0.82, 1.66). Recurrence [0.47 (0.34, 0.65)] was significantly lower and sustained cure rates [1.75 (1.35, 2.27)] significantly higher for fidaxomicin than vancomycin. Similar results were obtained in patient subgroups with severe CDI and with non-severe CDI. From the indirect comparison, the likelihood of recurrence [0.42 (0.18, 0.96)] and sustained cure [2.55 (1.44, 4.51)] were significantly improved for fidaxomicin versus metronidazole. Again, similar results were obtained in those with severe and non-severe CDI.

Conclusions: Fidaxomicin provides improved sustained cure rates in patients with CDI compared with vancomycin. An indirect comparison indicates that the same is also true for fidaxomicin versus metronidazole. In view of these data, fidaxomicin may be considered as first-line therapy for CDI.

Keywords: *C. difficile*, CDIs, treatment

Introduction

Dramatic changes in the epidemiology of *Clostridium difficile* infection (CDI) in recent years mean that it is now a major public health concern.1 There was a marked increase in its incidence in Europe, the USA and Canada during the 2000s. In addition, the infections have become more severe and there has been a rise in the number of cases in populations previously thought to be at low risk.2 The increase in incidence was attributable mainly to the emergence of a new, hypervirulent strain of *C. difficile*, BI/NAP1/027 (027), which produces more toxin than other strains.1,2 The prevalence of this strain is starting to decrease in some countries;3,4 however, this has been accompanied by the emergence of new hypervirulent strains, such as 078.5–7 As *C. difficile* is proving to be genetically facile, this pattern is likely to continue in the future.1

It is estimated that ~3% of healthy adults are colonized with *C. difficile*, which increases to up to 35% in hospitalized patients.8 In those residing in long-stay care facilities, CDI prevalence rates may be as high as 50%.9 The symptoms of CDI can range from mild diarrhea to abdominal pain, fever and leukocytosis and complications include pseudomembranous colitis, toxic megacolon, septic shock and bowel perforation.10,11 Approximately 6% of all patients with CDI experience complications, which rises to
Recurrence rates in those with CDI are high: ~20% – 25% of patients have recurrent disease after treatment is stopped.\(^{15}\) Furthermore, the risk is cumulative with a higher recurrence rate in those with previous recurrence.\(^{16,17}\) Consequently, repeated, prolonged treatment is often necessary. Epidemiological risk factors for recurrence include advanced age, continuation of antibiotics and prolonged hospital stays, while mechanistic risk factors include an inadequate immune response and persistent disruption of the normal colonic flora.\(^{16}\) Recurrences are of particular clinical importance in the elderly and frail subgroups (e.g. those with renal impairment\(^{18}\) or cancer\(^{19}\)).

CDI is associated with a significant economic burden, which is driven mainly by the costs of hospitalization.\(^{20,21}\) Across studies, the increase in duration of hospital stay due to CDI ranges from 3.6 to 21.3 days.\(^{14,20–27}\) The actual costs associated with CDI vary between studies and are estimated to be between ~£2900\(^{21}\) and ~£4107\(^{20}\) per patient in the UK. The economic burden of CDI in Europe has been reviewed extensively.\(^{28}\)

Treatment of the index episode of CDI is determined by the severity of symptoms; metronidazole is the mainstay of treatment for mild to moderate infection and vancomycin for severe episodes.\(^{29,30}\) However, neither drug is ideally suited for treatment of recurrent infection as metronidazole is associated with CNS neurotoxicity\(^{31}\) and both drugs are associated with a high recurrence rate (~25% – 30%)\(^{17}\) due to perturbations in intestinal flora.

Fidaxomicin (Dificlira\textsuperscript{TM}, Astellas) is the first representative of a new class of antibacterials, the macrocycles, characterized by an 18-membered macrocyclic ester structure and inhibitory activity against bacterial RNA polymerase.\(^{33}\) In vitro, fidaxomicin is at least eight times more active than vancomycin against clinical isolates of \emph{C. difficile}, including 027 strains.\(^{34–36}\) Other properties of fidaxomicin include minimal systemic absorption\(^{37}\) and limited activity against components of the normal gut flora in vitro\(^{33–35,38}\) and in vivo.\(^{38}\)

The aim of the current literature-based analysis was to evaluate the clinical efficacy of fidaxomicin versus the alternative standard of care (metronidazole and vancomycin) for the treatment of CDI.

### Methods

#### Study selection

Literature searches were performed between 27 July and 20 August 2011 to identify relevant studies and a second search was carried out on 3 July 2013 to update the findings. The literature databases and the search terms used are summarized in Tables S1 and S2 (both available as Supplementary data at JAC Online). No methodological limitations (including publication date) or filters were applied to the searches, although only articles in English were considered for data extraction. The database searches were supplemented by hand-searching of the bibliographies and abstracts of retrieved records.

The following measures were taken to ensure the rigour of the search and the selection of all relevant studies: the protocol for the search strategy was determined \emph{a priori} and complied with the requirements of the Scottish Medicines Consortium\(^{39}\) and the National Institute for Health and Clinical Excellence (NICE);\(^{40}\) the methodological quality of randomized controlled trials and observational studies was assessed using the criteria recommended by NICE and the Centre for Reviews and Dissemination;\(^{41}\) non-analytical studies (e.g. case studies and case series) and expert opinion pieces were not included; and the selection of studies for data extraction was conducted by two independent reviewers (Montserrat Casamajor and Cristina Ivanescu, Quintiles Consulting, The Netherlands). If available data were insufficient, the corresponding author of the study was contacted to determine whether the data could be obtained.

### Efficacy endpoints

The following efficacy endpoints were evaluated for both analyses: clinical cure (resolution of symptoms and no need for further therapy up to the second day after the end of treatment); recurrence (diarrhoea and a positive result on a stool toxin test any time after the end of treatment); and sustained cure (clinical cure in the absence of any recurrence during the follow-up period) (Figure 1). Recurrence could include relapse (same strain) and reinfection (different strain from index episode). In order to align the fidaxomicin studies with the non-fidaxomicin studies, patients with clinical cure who were lost to follow-up or died after the end of treatment were considered to have sustained cure unless a recurrence was reported before loss to follow-up; as reported in a paper published after the current analysis was conducted, this approach did not affect the sustained cure rates for fidaxomicin, but tended to benefit vancomycin.\(^{42}\)

### Efficacy of fidaxomicin versus vancomycin

Direct comparative studies of fidaxomicin and vancomycin were identified and used to evaluate the efficacy of these agents for CDI. In addition, a meta-analysis of data from the direct comparative trials was conducted, both in the overall populations and in specific patient subgroups (non-severe CDI, severe CDI and first recurrence). For the meta-analysis, the OR was used as the metric of choice. Between-study heterogeneity was evaluated with the \(\chi^2\) test-based \(Q\) statistic and was considered statistically significant at a level of 0.10. We further quantified the effect of heterogeneity across the studies using the \(I^2\) statistic following the guidance of Higgins et al.\(^{43}\) A naive categorization of values for \(I^2\) would not be appropriate for all circumstances, although we tentatively assigned adjectives of low, moderate and high to \(I^2\) values of 25%, 50% and 75%, respectively.

![Figure 1. Clinical cure, recurrence and sustained cure.](image-url)
Random-effects models were used where \( I^2 \) was \( \geq 50\% \). Data were analysed using Comprehensive Meta-Analysis Version 2 (Biostat Inc., Englewood, NJ, USA).

**Efficacy of fidaxomicin versus metronidazole**

From the literature searches conducted, there were no direct comparative studies of fidaxomicin and metronidazole for CDI. For this reason, their relative efficacy was assessed using an adjusted indirect comparison of trials that evaluated fidaxomicin versus vancomycin and metronidazole versus vancomycin.

Adjusted indirect comparisons were performed to yield estimates of the relative differences between fidaxomicin and metronidazole, using vancomycin as a data bridge. To conduct the adjusted indirect comparison for each of the three outcomes of interest, a traditional pairwise meta-analysis was performed for fidaxomicin versus vancomycin and a second such meta-analysis was carried out for metronidazole versus vancomycin. The methodology of Bucher et al.\(^{44}\) was employed to convert the summary estimates (log ORs) and measures of uncertainty (variances) from the two meta-analyses into an OR and 95% CI representing the difference between fidaxomicin and metronidazole. The null hypothesis was \( \text{OR}_{BC} = 1 \) (null relative effect of C versus B) versus the alternative hypothesis \( \text{OR}_{BC} \neq 1 \) (non-null relative effect of C versus B), where C = fidaxomicin and B = metronidazole. The methodology of Bucher et al.\(^{44}\) is a commonly used and well-validated technique for performing adjusted indirect comparisons using a third therapy as a common comparator.\(^{45,46}\)

**Results**

**Search results**

The number of articles identified by the literature searches conducted in 2011 and 2013 are shown in Figures S1 and S2 (both available as Supplementary data at JAC Online).

Overall, 36 studies were identified that evaluated the efficacy of fidaxomicin, metronidazole or vancomycin for CDI. Of these, 2 were direct comparative studies of fidaxomicin and vancomycin (\( n = 1164 \))\(^{47,48}\) and 11 studies compared the efficacy of vancomycin and metronidazole\(^{49-58}\) (Table S3, available as Supplementary data at JAC Online); the remaining 23 studies were not direct comparative studies of these agents. Three vancomycin versus metronidazole studies were included in the meta-analysis (\( n = 345 \))\(^{56-58}\) reasons for exclusion of the other studies are shown in Table S3. The duration of the follow-up period (after treatment discontinuation) was 28 days in the two fidaxomicin versus vancomycin studies,\(^{47,48}\) 21 days in two of the metronidazole versus vancomycin studies\(^{56,58}\) and 30 days in the remaining metronidazole versus vancomycin study.\(^{57}\)

**Efficacy of fidaxomicin versus vancomycin**

**Individual comparative studies**

Clinical cure rates, recurrence rates and sustained cure rates for the two identified studies (Study 003 and Study 004) are shown in Table 1. In both studies, fidaxomicin was non-inferior to vancomycin for clinical cure. The median time to resolution of symptoms for fidaxomicin and vancomycin was 58 and 78 h, respectively, in Study 003 and 50 and 48 h, respectively, in Study 004. Recurrence rates were significantly lower with fidaxomicin than vancomycin in both studies. This was accompanied by a significantly longer time to recurrence with fidaxomicin versus vancomycin: 20 days versus...
8 days in Study 003 ($P=0.003$) and 18 days versus 8 days in Study 004 ($P<0.0001$) (10% percentile data; analysed using the Wilcoxon test). Sustained clinical cure rates were significantly higher with fidaxomicin than vancomycin in both studies.

**Meta-analysis of comparative studies**

Study 003 and Study 004 had the same design and dosage regimens. In addition, the treatment arms of both studies were well balanced in terms of demographics and baseline characteristics.

Cure was achieved in 88% of patients receiving fidaxomicin compared with 86% of patients receiving vancomycin; the corresponding OR (95% CI) was 1.17 (0.82, 1.66) (heterogeneity: $\chi^2=0.126$, df=1, $P=0.723$, $I^2=0.0\%$). Recurrence rates and sustained cure rates were significantly better with fidaxomicin than vancomycin (Figure 2a). Recurrence rates were 13% with fidaxomicin and 24% with vancomycin; OR (95% CI) = 0.47 (0.34, 0.65) (heterogeneity: $\chi^2=0.855$, df=1, $P=0.355$, $I^2=0.0\%$). Sustained cure rates were 76% and 64%, for fidaxomicin and vancomycin, respectively; OR (95% CI) = 1.75 (1.35, 2.27) (heterogeneity: $\chi^2=0.267$, df=1, $P=0.606$, $I^2=0.0\%$). OR data for the individual studies are shown in Table 1.

The results of the meta-analysis according to patient subgroup are shown in Figure 2(b) and the results from the individual studies are shown in Table S4 (available as Supplementary data at JAC Online). Recurrence rates were significantly lower with fidaxomicin versus vancomycin in those with severe and non-severe CDI. Results for sustained cure were significant in the non-severe subgroup; in the severe subgroup, the 95% CI was 0.99–2.26.

**Figure 2.** Forest plot for (a) overall population and (b) patient subgroups for clinical cure, recurrence and sustained cure for fidaxomicin versus vancomycin based on meta-analysis of data from Study 003 and Study 004.47,48

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI)</th>
<th>Severe CDI</th>
<th>Non-severe CDI</th>
<th>First recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td>1.49 (0.99, 2.26)</td>
<td>1.92 (1.37, 2.69)</td>
<td>1.67 (0.89, 3.13)</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>0.46 (0.26, 0.79)$^a$</td>
<td>0.49 (0.32, 0.74)$^a$</td>
<td>0.53 (0.26, 1.09)</td>
<td></td>
</tr>
<tr>
<td>Sustained cure</td>
<td>0.86 (0.50, 1.47)</td>
<td>1.45 (0.63, 3.36)</td>
<td>1.08 (0.42, 2.81)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Significant difference between fidaxomicin and vancomycin (95% CI excludes 1).
**Efficacy of fidaxomicin versus metronidazole**

In the meta-analysis of the three vancomycin versus metronidazole studies, cure rates were 88% and 81%, respectively, recurrence rates were 9% and 10%, respectively, and sustained cure rates were 79% and 71%, respectively, in the overall population. There were no statistically significant differences in any of these parameters (Figure 3a). Clinical cure and sustained cure rates were significantly higher for vancomycin versus metronidazole in those with severe CDI (Figure 3b).

The indirect comparison showed that the likelihood of recurrence and sustained cure was significantly improved for fidaxomicin versus metronidazole in the overall CDI population (Figure 4). Similar results were obtained in those with severe CDI. In non-severe infection, sustained cure rates were significantly higher for fidaxomicin versus metronidazole.

**Discussion**

Metronidazole and vancomycin form the mainstay of treatment for CDI, the former for mild or moderate episodes and the latter for severe CDI episodes. Fidaxomicin is the first in a new class of macrocycle antibiotics with a favourable profile for treating CDI:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td>1.73 (0.93, 3.20)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0.88 (0.41, 1.92)</td>
</tr>
<tr>
<td>Sustained cure</td>
<td>1.46 (0.88, 2.42)</td>
</tr>
</tbody>
</table>

(a) Vancomycin versus metronidazole

(b) Vancomycin versus metronidazole

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td></td>
</tr>
<tr>
<td>Severe CDI</td>
<td>9.31 (1.11, 78.2)</td>
</tr>
<tr>
<td>Non-severe CDI</td>
<td>4.22 (0.45, 39.49)</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
</tr>
<tr>
<td>Severe CDI</td>
<td>0.43 (0.10, 1.90)</td>
</tr>
<tr>
<td>Non-severe CDI</td>
<td>0.61 (0.10, 3.89)</td>
</tr>
<tr>
<td>Sustained cure</td>
<td></td>
</tr>
<tr>
<td>Severe CDI</td>
<td>4.40 (1.28, 15.14)</td>
</tr>
<tr>
<td>Non-severe CDI</td>
<td>2.54 (0.61, 10.61)</td>
</tr>
</tbody>
</table>

*Data for severe and non-severe subgroups from Zar et al. only; the number of patients in the metronidazole and vancomycin groups were 38 and 31, respectively (severe CDI), and 41 and 40, respectively (non-severe CDI).

*Significant difference between vancomycin and metronidazole (95% CI excludes 1).
it has a narrow-spectrum antibacterial profile and potent bactericidal activity against C. difficile. Furthermore, it undergoes minimal absorption and exerts its activity within the gastrointestinal tract.

Two Phase III studies with similar designs have been conducted to compare the efficacy of fidaxomicin with that of vancomycin. The results of these studies indicate that fidaxomicin is associated with minor improvements in clinical cure rates versus vancomycin and significant improvements in recurrence rates, time to recurrence and sustained cure. These results were confirmed in the current meta-analysis of the two studies and likely reflect the pharmacological profile of fidaxomicin (and in particular its limited activity against the normal gut flora). As discussed in the accompanying paper, the clinical benefits of fidaxomicin translate into pharmacoeconomic advantages despite its higher acquisition costs versus vancomycin. The results obtained for fidaxomicin versus metronidazole were similar to those for fidaxomicin versus vancomycin in both severe and non-severe CDI. There was also a significant difference between treatments in favour of fidaxomicin for sustained cure in the non-severe subgroup; in the severe group, this approach showed significance (the lower 95% CI was 0.99). There were no significant between-group differences in outcomes in patients with a first recurrence.

To compare fidaxomicin and metronidazole, an indirect comparison was made using data from meta-analyses of studies of fidaxomicin versus vancomycin and vancomycin versus metronidazole. The results obtained for fidaxomicin versus metronidazole were similar to those for fidaxomicin versus vancomycin. There were no statistically significant between-group differences in clinical cure rates; however, fidaxomicin was associated with significantly lower recurrence rates and significantly higher sustained cure rates than metronidazole in the overall CDI population. Once again, the positive effect of fidaxomicin on sustained cure rates versus metronidazole likely reflects its limited effect on the normal gut flora. The results of the subgroup analyses, which showed significantly higher sustained cure rates for fidaxomicin versus metronidazole in severe and non-severe CDI (as well as significantly lower recurrence in severe CDI), should be interpreted with caution given the smaller patient numbers (and hence wide CIs).

The mechanism of action of the positive impact of fidaxomicin on recurrences has not yet been elucidated. As discussed above, it likely reflects the lack of a perturbing effect of fidaxomicin on the normal gut flora, a feature that differentiates it from vancomycin and metronidazole. Consequently, it does not create a favourable environment for any persistent C. difficile spores to germinate in the gut. In addition, compared with vancomycin, fidaxomicin has substantially higher inhibitory activity against C. difficile and a more prolonged post-antibiotic effect. Also, fidaxomicin is bactericidal whereas vancomycin is bacteriostatic and this may contribute to the lower risk of recurrence with fidaxomicin.

There are a number of limitations associated with the current analyses. Only five studies with sufficient data were identified for inclusion in the meta-analyses, two comparing fidaxomicin and vancomycin and three comparing vancomycin and metronidazole. For the latter, only one was double blind and placebo controlled. Two additional studies, which compared with tolevamer, vancomycin and metronidazole, were not included as the data were available only in abstract form at the time of the analysis—future indirect comparisons could therefore be conducted to evaluate the comparative efficacy of fidaxomicin and other treatments such as tolevamer and faecal microbial transplantation. Despite the inclusion of only a small number of studies, an indirect comparison can nevertheless render correct point estimates, although the precision of the estimates will be low. Another limitation is differences in the inclusion criteria between the three vancomycin versus metronidazole studies.
the comparative efficacy of vancomycin and metronidazole in reported outcomes between studies, depending on factors such as study design, location and follow-up period.

In conclusion, the current analyses indicate that fidaxomicin offers significant benefits in terms of patient outcomes compared with vancomycin. Indirect comparisons indicate that the same is also true for fidaxomicin compared with metronidazole. These data suggest that in the absence of a randomized controlled trial of fidaxomicin versus metronidazole, fidaxomicin should be considered as a potential first-line treatment for CDI, rather than as a second- or third-line treatment after vancomycin and metronidazole. The results also support the first-line use of fidaxomicin in those with severe infection. Further analyses of fidaxomicin versus metronidazole in non-severe disease, including a comparison of safety and tolerability, are required.

Funding
This work was supported by Astellas Pharma Europe Ltd. Writing and editorial assistance in the preparation of this manuscript, which was provided by Bioscript Medical, was funded by Astellas. The work of Quintiles Consulting was also funded by Astellas Pharma Europe Ltd.

Transparency declarations
O. A. C. is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN1106) and has received research grants from, is an advisor to or has received lecture honoraria from 3M, Actelion, Astellas, Basilea, Bayer, Celgene, Cubist, F2G, Genzyme, Gilead, GSK, Merck/Schering, Miltenyi, Optimer, Pfizer, Quintiles, Sanofi Pasteur, Summit and Viropha. D. N. has received lecture or advisory board honoraria or research grants from Astellas, AstraZeneca, Bayer, Basilea, Cubist, Durata and Pfizer. He has received no remuneration for this manuscript. The views expressed and findings presented by D. N. are personal and not the views of the Scottish Antimicrobial Prescribing Group that he chairs. C. I. is employed by Quintiles Consulting. O. O.-S. and I. A. O. O. are employees of Astellas Pharma Europe Ltd, and do not own stocks or options in Astellas Pharma Ltd. P. R. was employed by Astellas Pharma Europe Ltd at the time of the analysis, and is now employed by Merck.

The development of the manuscript, editing and submission assistance for this manuscript was provided by Nicky French of Bioscript Medical.

Supplementary data
Tables S1 to S4 and Figures S1 and S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


