Real world evaluation of the introduction of fidaxomicin (DIFICLIR™▼) for the management of *Clostridium difficile* infection in seven NHS secondary care Trusts in England

Introduction

Clostridium difficile infection (CDI) remains an important healthcare issue in the UK, with 16,947 reported cases between April 2013 and March 2014.[1,2,3,4]

The National Institute of Health and Care Excellence (NICE) recommends that when deciding on a treatment for CDI, the local decision maker should consider the medical need, potential benefits, risks of treatment and cost of treatment.[5] Guidance from Public Health England recommends fidaxomicin as an initial treatment option for severe cases of CDI in patients at high risk for recurrence; in addition, fidaxomicin is the preferred treatment for recurrent CDI.[6]

Fidaxomicin is an oral macrocyclic antibiotic, licensed in the EU in December 2011, and launched in the UK in June 2012, for the treatment of CDI in adults.[7] Its bactericidal activity is targeted towards *C. difficile*, with minimal impact on the colonic microflora.[7] *In vitro*, fidaxomicin has been demonstrated to inhibit spore and toxin production.[8,9] Whilst fidaxomicin has not been compared directly with metronidazole in clinical trials, fidaxomicin was found to be non-inferior to vancomycin in curing patients with mild to severe CDI in a phase 3 study.[10] Furthermore, significantly more patients remained symptom-free in the 28 days after treatment with fidaxomicin compared with oral vancomycin.[11] The safety profile of fidaxomicin appeared similar to that of oral vancomycin.[5,10,11]

Methods[12]

The introduction of fidaxomicin into NHS secondary care Trusts was evaluated to collect robust real world data regarding the cost-effectiveness of fidaxomicin when introduced into routine clinical practice at various positions in the treatment pathway.

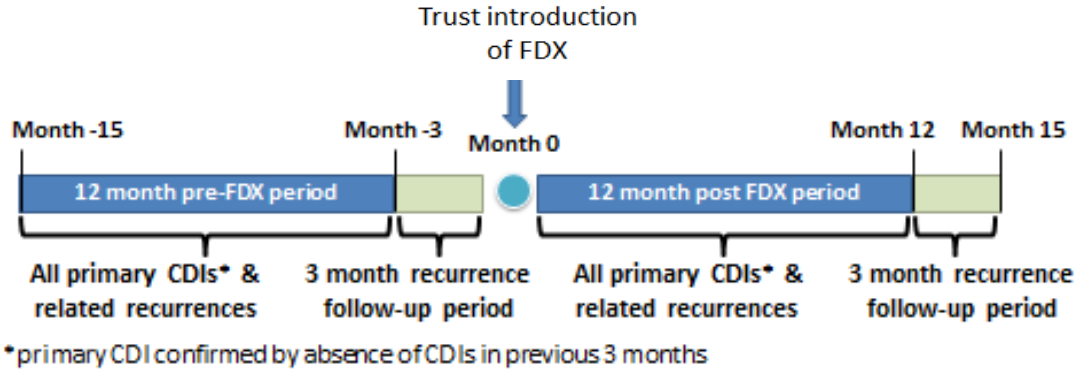
The evaluation involved two retrospective observation periods:

1. The first was conducted **prior** to the local introduction of fidaxomicin, and included all patients who had a confirmed primary CDI during this period.
2. The second observation period occurred **after** the introduction of fidaxomicin, and included all patients who had a confirmed primary CDI in this period.

CDI recurrence was defined as the re-emergence of CDI symptoms (judged by the frequency of three or more passed unformed stools), with or without a positive toxin test, with a clinical decision to re-treat within 3 months of the previous case.

In order to confirm that episodes were primary infections in the period before the introduction of fidaxomicin, the pre-evaluation period started 15 months prior to the introduction of fidaxomicin at each Trust. The post-evaluation period identified all primary cases in the 12 months after the

introduction of fidaxomicin and followed the final patients for a further 3 months in order to capture any recurrences (Figure 1).



All patients with a positive toxin A or B, or both, test for *C. difficile* within the evaluation period (pre- and post-adoption of fidaxomicin) were identified from microbiology department records. The following eligibility criteria for primary episodes were subsequently applied in order to narrow the patient population:

- Male or female inpatients
- Patients who were aged ≥18 years at the time of the positive CDI sample
- Patients who had CDI as defined by:
    - Diarrhoea, which was defined as a change in bowel habits with three or more unformed bowel movements
    - Confirmed CDI (presence of either toxin A or B, or both, of *C. difficile* in the stool)

Data regarding each case of CDI were collected from hospital systems and medical notes using a pre-specified data collection form. The information collected included patient characteristics, CDI severity, date of onset and resolution, resource use/cost utilisation and CDI treatments.

Data analysis was pooled via the following evaluation groupings:

In the pre-FDX period:

- All episodes of CDI treated with vancomycin or metronidazole, before introduction of FDX (n=798)

In the post-FDX period:

- FDX 1st line; all episodes of CDI treated first line with FDX – defined as FDX started as first treatment or within ≤24 hours of another agent (n=177)
- FDX not 1st line; all episodes of CDI treated with FDX not first line – defined as FDX started after ≥24 hours of another agent or agents (n=80)
- Non-FDX; all episodes of CDI not treated with FDX (n=411)

Results[12]

Analyses pooled from seven trial centres across England were presented at the 5th International *Clostridium Difficile* Symposium (ICDS) in Bled, Slovenia, 2015. Patterns of fidaxomicin use differed between the seven centres, with centres A and B treating with fidaxomicin as first-line treatment for all patients and the other five centres using fidaxomicin as first-line treatment only in selected patients for both primary and recurrent CDI. The results showed that the most optimal recurrence, all-cause mortality, and cost effectiveness was seen when fidaxomicin was used first-line for all, and not restricted to selected patients only. This suggests that the pattern of adoption of fidaxomicin appears to affect its impact on CDI outcomes, and is an increasingly important result as in-patient recurrence remains a challenge in the context of current infection control efforts against CDI within the UK and Europe.[13]

The analysis for two of the centres (centres A and B) found that when using fidaxomicin first-line in all patients:

- 28-day all-cause mortality rates dropped significantly
- In both centres recurrence rates fell from 12.1% and 23.5% with standard of care treatments to 3.1% with fidaxomicin
- 5 and 10 recurrences could be avoided for every 50 patients treated in centres A and B respectively, resulting in a cost saving of £19,490 in centre A, and £121,144 in centre B
- With 16,947 cases of CDI reported in the UK between April 2013 and March 2014,[1,2,3,4] potential for cost saving is likely to be far greater.

Discussion[12]

This evaluation shows that cost outcomes may be improved with first-line use of fidaxomicin compared with other treatment options, through the avoidance of episodes of recurrence. This evaluation also shows that where fidaxomicin has been introduced as part of a stratified CDI treatment protocol, it tends to be reserved for the most severe cases of CDI, whilst those with non-severe CDI are more likely to receive an alternative treatment option.[14] Despite the increased CDI severity in the fidaxomicin-treated patients compared with patients not treated with fidaxomicin, a lower recurrence rate was associated with fidaxomicin compared with the pre-fidaxomicin group.

The overall high mortality rate for all groups highlights the importance of treating CDI promptly and effectively.[14] It is therefore important to note that the greatest reductions in recurrence rates post-fidaxomicin were observed in hospitals treating all patients with fidaxomicin first-line. Additionally, lower 28-day all-cause mortality was observed when fidaxomicin was used in the first-line setting compared with the pre-fidaxomicin period.

Although the acquisition cost of fidaxomicin is greater than that of older, broad-spectrum generic treatment options, this evaluation illustrates that the savings gained by avoiding the costs associated with treating episodes of CDI recurrence far outweigh the incremental cost of fidaxomicin.

Conclusion[12]

This evaluation showed that the impact of fidaxomicin on CDI outcomes was influenced by local patterns of adoption, with the most optimal results in terms of recurrence rate, all-cause mortality and cost effectiveness observed in hospitals using fidaxomicin as first-line treatment in all CDI patients, rather than in selected patients only.

This evaluation has demonstrated that using fidaxomicin first-line has the potential to improve outcomes for this vulnerable group of patients.

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References

1. Public Health England, *Clostridium difficile* infection: annual data. *C. difficile* infections: quarterly counts by acute trust and CCG and financial year counts and rates by acute trust and CCG, May 2014. Available online via: https://www.gov.uk/government/statistics/clostridium-difficile-infection-annual-data (Last accessed May 2015).
2. Health Protection Scotland, Quarterly report on the surveillance of *Clostridium difficile* infection in Scotland, January - March 2014. July 2014. Available online via: http://www.hps.scot.nhs.uk/haiic/sshaip/publicationsdetail.aspx?id=50174 (Last accessed May 2015).
3. HSCNI Public Health Agency, Summary Tables for *Clostridium difficile* and MRSA (Meticillin Resistant Staphylococcus aureus) cases 2006/07 to 2014/15 Available online via: http://www.publichealth.hscni.net/sites/default/files/End%20August%202014.pdf (Last accessed May 2015).
4. Public Health Wales. *Clostridium difficile* and Staphylococcus aureus Bacteraemia Monthly Update. Available at: http://www.wales.nhs.uk/sites3/page.cfm?orgid=379&pid=67899 (Last accessed May 2015).
5. NICE. *Clostridium difficile* infection: fidaxomicin. 13 July 2012. Available from: http://www.nice.org.uk/advice/esnm1. (Last accessed May 2015).
6. Public Health England, Updated guidance on the management and treatment of *Clostridium difficile infection*, May 2013. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/321891/Clostridium_difficile_management_and_treatment.pdf. (Last accessed May 2015).
7. DIFICLIR (fidaxomicin) Summary of Product Characteristics.
8. Babakhani F, *et al.* Fidaxomicin inhibits spore production in *Clostridium difficile*. *Clin Infect Dis* 2012; 55(S2): S162–169.
9. Babakhani F, *et al*. Fidaxomicin inhibits toxin production in *Clostridium difficile. J Antimicrob Chemother.* 2013; 68: 515–522.
10. Cornely O, *et al*. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Diseases*. 2012;12(4):281-9.
11. Cornely O, *et al*. Treatment of First Recurrence of *Clostridium difficile* Infection: Fidaxomicin Versus Vancomycin. *Clin Infect Dis* 2012; 55(S2): S154–161.
12. Howard P, *et al*. The impact of the introduction of fidaxomicin on the management of *Clostridium difficile* infection in 7 NHS secondary care Trusts in England. Presented at ICDS 2015.
13. Bauer MP, *et al.* European Society of Clinical Microbiology and Infectious Disease (ESCMID): treatment guidance document for *Clostridium difficile*-infection (CDI). *Clin Microbiol Infect*. 2009;15:1067-79.
14. Data on file DIF14106UK(1). Astellas Pharma Ltd. November 2014.