1 ABSTRACT

Title

A drug utilisation study (DUS) of the use of oral fidaxomicin in the routine clinical setting (2819-CL-2002) ("ANEMONE")

Keywords

Fidaxomicin; *Clostridium difficile* infection; Post-authorisation Safety Study; Drug Utilisation

Rationale and background

Fidaxomicin, a novel antibiotic agent, is approved in the United States (US) (2011) and in the European Union (EU) (2012) for the treatment of *Clostridium difficile* infection (CDI), also known as *Clostridium difficile*-associated diarrhoea (CDAD), in adults.

In the clinical development program, information on specific patient populations is limited or not available. These specific populations are patients with concomitant inflammatory bowel disease (IBD), fulminant or life-threatening CDI, severe renal impairment, moderate or severe hepatic impairment and pregnant patients. These patient populations are considered missing information in the fidaxomicin Risk Management Plan (RMP).

The objective of this drug utilisation study (DUS) was to collect post-authorisation information to assess the use of fidaxomicin in a routine clinical setting and to further assess safety characteristics (i.e., the events of death, and laboratory and electrocardiogram [ECG] results on specific time points) in patient populations with medical conditions of specific interest (MCSIs; i.e., IBD, fulminant or life-threatening CDI, severe renal impairment, moderate or severe hepatic impairment and pregnancy) and in the overall population.

This DUS is a post-authorization study to further assess the use of fidaxomicin in standard clinical practice, and part of the RMP, agreed with the European Medicines Agency.

Research question and objectives

Primary Objective

The primary objective of this study was to estimate the proportion of patients with an MCSI of the total study population treated with fidaxomicin.

Secondary Objectives

- To collect the events of death, laboratory and ECG data at specific time points (i.e., at admission, before the first dose of fidaxomicin, at the time of the last dose of fidaxomicin and at the end of the observation period) in patients with a condition of interest and of the overall population;
- To collect information on the use of fidaxomicin related to indication, dose and duration of use in patients with a condition of interest and in the overall population;

- To collect data on the response to fidaxomicin treatment in the routine clinical setting in patients with a condition of interest and in the overall population.

Study design

This was a multi-centre, multi-national, post-authorisation, retrospective chart review.

Medical records of adult patients who, according to the pharmacy records of the study sites, were prescribed fidaxomicin during the (country-specific) eligibility period, were reviewed retrospectively to collect information for this study.

The country-specific eligibility period was defined as the period between first launch of fidaxomicin in a country and the date the first site in the country was contacted (i.e., the index date). Each patient could have received more than 1 treatment episode with fidaxomicin. An episode was considered distinct from the previous episode if separated by more than 30 days from the last dose of the previous treatment episode to the first dose of the subsequent treatment episode. Unless otherwise specified throughout, the unit of analysis was treatment episode and not patient. Therefore, results were described using the term "treatment episode" or, when applicable, by "patient".

Prespecified data points included in the medical records from the patient's hospital admission up to 30 days after the last dose of fidaxomicin (the patient's observational period) were collected. In the absence of last dose of fidaxomicin (and any other actual fidaxomicin administration information), the observational period ended 40 days after the date fidaxomicin was last prescribed.

Setting

Country selection criteria included available prescription data, the number of prescribers per capita, and the regulatory path to allow the conduct of observational studies and collection of data anonymously (i.e., waiver of consent). The final selected countries were Spain, Germany, the United Kingdom (UK) and Austria.

Patient and study size, including dropouts

Initially 2 to 4 sites per country were targeted for a total of 10 to 15 sites. However, the number of patients per site was very heterogeneous and some sites had initially overestimated the number of eligible patients. In total, 68 sites were contacted; of these, 38 sites were not interested, 3 were not selected, 3 did not respond, and 2 declined. The actual number of sites selected was 22 (2 from Austria, 6 from Germany, 6 from Spain and 8 from the UK).

The following criteria had to be met in order for a patient to be included in the study:

Inclusion Criteria

- Patients aged ≥ 18 years;
- Patients for whom the time of prescription of fidaxomicin and their entire corresponding observational period fell within the (country-specific) eligibility period.

Exclusion Criterion

- Patients who participated in a clinical study with fidaxomicin.

At each site, data from up to 50 eligible patients were to be included in the study. If there were more than 50 eligible patients at a site, only 50 patients were randomly selected for inclusion in order to avoid a cluster effect and possible oversampling that could impact representativeness of the results.

Variables and data sources

The following information from the medical records, upon availability, was recorded in the electronic case report form (eCRF):

- Demographics and anthropometrics;
- Hospital admission history;
- History of diarrhoea (in the 3 months prior to the first dose of fidaxomicin);
- Indication for fidaxomicin treatment;
- CDI characteristics (confirmation, symptoms, treatment);
- Fidaxomicin exposure (dose and duration);
- Additional medication;
- MCSIs: IBD, fulminant or life-threatening CDI (defined according to a scoring system based on Debast et al [2014] and also defined according to investigator judgement), moderate and severe hepatic impairment, severe renal impairment and pregnancy;
- Safety measurements:
    - Death,
    - Laboratory assessments at specific time points,
    - ECG assessments;
- Response to fidaxomicin treatment.

Results

Of the 582 patients exposed to fidaxomicin who were enrolled retrospectively between June 2012 and June 2015, 6 patients were excluded: 4 because their observational period did not fall within the (country-specific) eligibility period and 2 patients due to a failure to properly complete patient information forms. Therefore, 576 patients' data were analysed in 4 European countries: 68 in Austria, 105 in Germany, 118 in Spain and 285 in the UK. The average age of the patient population was about 69 years, ranging from 18 to 99 years of age, with 42.2%, of patients being 75 years of age or older. Patients were equally distributed with respect to gender and 84.5% of patients were of white ethnicity.

Prevalence of MCSIs:

In the overall population:

- IBD was reported in 5.0% (29 of 576) of patients (95% CI: 3.4, 7.2).
- According to the PI judgement, 15.1% (87 of 576) of patients (95% CI: 12.3, 18.3) presented with fulminant CDI (CDI-PI).

- According to the scoring system 19.8% (114 of 576) of patients (95% CI: 16.6, 23.3) presented with fulminant CDI (CDI-SS).
- Severe renal impairment was present in 18.1% (104 of 576) of patients (95% CI: 15.0, 21.4).
- Moderate or severe hepatic impairment was present in 8.7% (50 of 576) of patients (95% CI: 6.5, 11.3).
- No pregnancy was reported in the patients included in the study.

The categorization of patients was not mutually exclusive and patients could belong to more than one category.

Safety outcomes

Deaths

During the observation period, 25.3% of the study population died (146 of 576). Of the 120 deaths with information about the cause of death, 24.2% (29 of 120) were attributed to CDI. Overall, 6% (24.2% x 25.3%) of the total patient population died in relation to CDI.

The mortality rate was slightly higher in patients with at least 1 MCSI (28.4%, 74 of 261) than in patients with no MCSI (22.9%, 72 of 315).

The mortality rate was lower in patients with IBD (17.2%, 5 of 29) than in patients with moderate or severe hepatic impairment (20.0%, 10 of 50), severe renal impairment (33.7%, 35 of 104) and fulminant CDI (34.2%, 39 of 114 for CDI-SS and 34.5%, 30 of 87 for CDI-PI). This could be expected as IBD patients tend to be younger and perhaps healthier than patients with fulminant CDI or severe levels of hepatic and renal impairment and these latter conditions are associated with a risk of severe organ failure and death.

The cause of death was attributed to CDI in more patients with at least 1 MCSI (37.7%, 23 of 61) than in patients with no MCSI (10.2%, 6 of 59). However, patients with at least 1 or more MCSIs present with a poorer overall health condition.

Laboratory results

Considering the decreasing number of laboratory parameters assessed over time, the observed variance and the small amount of data collected at the last timepoint, the changes observed in the laboratory parameters should be interpreted with caution.

- Overall population

The mean and median haemoglobin and haematocrit values were below the respective normal ranges of 140 to 175 g/L and 0.41 to 0.50 at the 4 time points. Low levels of hemoglobin and hematocrit are associated with an increased susceptibility to infection and therefore is not an unexpected finding that patients who contract CDI should have low values on these parameters. There was no effect of fidaxomicin treatment on these parameters.

The median overall white blood cell (WBC) counts were within the normal range of 4.5 to 11×10^9/L at all time points, whereas the mean WBC count was above the normal range prior to fidaxomicin treatment and within the normal range at the last dose of fidaxomicin and at

the end of the observation period. The difference in the mean and median WBC counts most likely reflects the heterogeneity of the CDI severity in the total study population. The reduction in both the mean and the median WBC counts following fidaxomicin treatment is consistent with the positive treatment response.

The mean and median blood urea nitrogen (BUN) levels were at or above the upper limit of the normal range of 2.9 to 8.2 mmol/L at the 4 time points. The mean BUN values were consistently higher than the median values. The median level of creatinine was within the normal range of 53 to 106 µmol/L whereas the mean creatinine values were above the upper normal limit at all 4 time points. This skewed distribution most likely reflects the heterogeneity of the renal function across the study population. There was no apparent effect of fidaxomicin treatment on BUN levels at the population level.

The mean and median sodium and potassium levels were within the respective normal ranges of 136 to 142 mmol/L and 3.5 to 5 mmol/L at the 4 time points for the overall population. There was no apparent effect of fidaxomicin treatment.

The median and the mean levels of total bilirubin were within the normal range of 5 to 21 µmol/L at the 4 time points in the overall population. The mean values were between 11.2 and 18.7 µmol/L whereas median values were around 7 to 8 µmol/L prior to fidaxomicin treatment to last dose. The median level of alkaline phosphatase (ALP) was within the normal range of 0.5 to 2.0 µkat/L whereas the mean values were slightly above the normal range at the 4 time points in the overall population. The median and mean levels of alanine aminotransferase (ALT) were within the normal range of 0.17 to 0.68 µkat/L at the 4 time points in the overall population. The median values were approximately 0.3 µkat/L prior to fidaxomicin treatment and at last dose whereas the mean values were around 0.5 µkat/L. The median level of aspartate aminotransferase (AST) was within the normal range of 0.17 to 0.51 µkat/L whereas the mean values were above the normal range at the 4 time points in the overall population. The median value was higher at the last dose of fidaxomicin (0.45 µkat/L, n = 127) than prior to fidaxomicin treatment (0.37 µkat/L, n = 208). This variability most likely reflects both the proportion of the total population with any degree of hepatic impairment (17% of the overall population) and the heterogeneity of hepatic function across the study population. There were no apparent effects of fidaxomicin on the hepatic function markers at the study population level.

The median glucose level was within the normal range of 70 to 110 mg/dL prior to fidaxomicin treatment (106.5 mg/dL), and at the upper normal range at last dose of fidaxomicin (110.5 mg/dL). The mean plasma glucose concentration was above the normal range at all time points. It was not possible to comment on the medical significance of the glucose levels as medical history was not collected as part of this study. There was no apparent effect of fidaxomicin treatment on plasma glucose at the population level.

The median and mean levels of serum albumin were below the normal range of 32 to 56 g/L prior to fidaxomicin treatment and at the last dose in the overall population. The hypoalbuminemia observed in the total population is certainly caused by acute and chronic

inflammatory responses in response to CDI. There was no apparent effect of fidaxomicin treatment on serum albumin at the population level.

- Laboratory results for MCSIs

The following can be noted regarding laboratory results for the MCSIs compared to the overall population.

Among patients with IBD, as observed in the overall population and in patients with no MCSI, the median haemoglobin and haematocrit levels were below the normal ranges at all time points. There was no apparent effect of fidaxomicin treatment on these parameters. The reduction in both the mean and the median WBC counts from admission and following fidaxomicin treatment is consistent with the positive treatment response in the IBD patient subgroup. Similar trends were observed for neutrophils and monocytes, again consistent with a positive response to treatment.

Among patients with fulminant CDI (according to either PI judgement or the CDI scoring system), there was a general trend toward reduction in mean WBC counts in the fulminant CDI subgroup and this was consistent with a positive treatment effect of fidaxomicin in this subgroup. Similar trends were observed for neutrophils.

The high creatinine levels observed in the fulminant CDI subgroup (with both categorisation methods) most probably reflects the relatively high proportion of patients with renal impairment in the fulminant CDI subgroup (around half of the patients presented with renal impairment of any severity level).

Among patients with severe renal impairment, as expected considering this condition, the median and mean BUN levels were above the normal range of 2.9 to 8.2 mmol/L at all time points. Nonetheless, as observed in the overall population and in patients with no MCSI, there was no apparent effect of fidaxomicin treatment on BUN levels in patients with severe renal impairment. Of note, the median creatinine level decreased from 237.55 µmol/L prior to fidaxomicin treatment (n = 88) to 183.38 µmol/L at the last dose (n = 62). This may be a consequence of improved systemic hydration rather than any direct improvement of renal function.

Among patients with moderate or severe hepatic impairment, the median total bilirubin slightly decreased from prior to fidaxomicin treatment (n = 40) to last dose (n = 25) while the contrary was observed for the mean values. Given the low number of observations, this skewed distribution is most likely due to chance rather than a reflection of the heterogeneity of hepatic function in this subgroup. Despite the low number of observations, there was no apparent effect of fidaxomicin treatment on liver enzyme levels in the patients with moderate or severe hepatic impairment. The observed increase in serum albumin after fidaxomicin treatment may be a consequence of the positive treatment effect of fidaxomicin in this subgroup.

ECG results

At admission, ECG results were available for 36.9% (218 of 590) of the overall treatment episodes. The proportion of available ECG results decreased over time: from 13.9% (82 of 590) prior to fidaxomicin treatment to 7.5% (44 of 590) afterwards, which may suggest that there were few reasons for additional ECGs to be administered. Due to the sparsity of data, the ability to draw meaningful observations is limited and the following observations should be regarded with caution.

The clinically significant abnormal ECGs represented 21.6% (47 of 218) of the treatment episodes where ECG was performed at admission. The proportion of clinically significant abnormal ECGs remained stable during the first 3 time points

In patients with MCSIs with sufficient available ECG results, the proportion of clinically significant abnormal ECGs remained stable or decreased from the last result before the first dose of fidaxomicin to the time of last fidaxomicin dose. Similar to the overall population, there was no apparent effect of fidaxomicin treatment on the proportion of clinically significant abnormal ECGs in patients with MCSIs.

Fidaxomicin exposure

Overall, there were 611 prescriptions in the 590 fidaxomicin treatment episodes. The standard prescription was for a period of 10 days.

Fidaxomicin was prescribed as 200 mg per intake in all the prescriptions and was taken twice daily in all prescriptions (100%) and was prescribed for confirmed CDI in almost all cases (97.5%, 596 of 611). Fidaxomicin was prescribed for prophylactic use in 8 cases, or for an unconfirmed infection in 7 cases. The fidaxomicin prescriptions followed the recommended dosing schedule (i.e., 200 mg twice daily for 10 days) for all MCSIs.

In the overall population, the mean duration of fidaxomicin intake per treatment episode was 10.3 days with a median of 11 days. The mean number of doses taken was 20.5 doses with a median of 22 doses. The recommended dose schedule of 200 mg of fidaxomicin twice daily for 10 days was observed for 73.1% (431 of 590) of the fidaxomicin treatment episodes.

In patients with IBD, the reported compliance with the recommended dosing schedule was higher (82.8% of treatment episodes, 24 of 29) than in patients with no MCSI (74.6% of treatment episodes, 238 of 319) or in patients with other MCSIs where it ranged from 64.2% of treatment episodes of fulminant CDI-SS to 74.5% of treatment episodes with moderate or severe hepatic impairment.

The variability observed between the different subgroups may be explained by the average number of doses taken which was slightly higher than the expected 20 doses (mean of 20.5) ranging from 19.7 doses in treatment episodes with IBD to 21.1 doses in treatment episodes of fulminant CDI-SS.

Fidaxomicin response

In the overall population, diarrhoea resolved in 78.0% (404 of 518) of treatment episodes, within a mean of 8.0 days (n = 347) and a median of 6.0 days from first dose of fidaxomicin. Diarrhoea recurred within 30 days after the end of fidaxomicin treatment in 18.8% (79 of 420) of the treatment episodes, and recurred on average 19 days later (n = 68). Diarrhoea resolved in a slightly higher proportion of treatment episodes in patients with no MCSIs and in patients with IBD, moderate or severe hepatic impairment and fulminant CDI-PI (67.5% to 83.3%), than in patients with severe renal impairment and fulminant CDI-SS (68% to 69%). The average time elapsed from the first dose of fidaxomicin to diarrhoea resolution varied between 6 and 8 days across MCSI.

The proportion of recurrence was similar in patients with MCSIs and in patients with no MCSI, except in treatment episodes of fulminant CDI-PI where it was slightly lower (13.9%, 10 of 72). The mean time to diarrhoea recurrence from last dose of fidaxomicin varied between 18 and 27 days, except for IBD which was 11.5 days (in 2 treatment episodes only).

Discussion

Patients with MCSI represented almost half of the study population (45.3%, 261 of 576).

This study shows that a large proportion (40%) of fidaxomicin patients had some renal impairment; and 18% of patients had severe renal impairment. This could be expected given that elderly patients represented the vast majority of the study population. Only 9% of patients had moderate or severe hepatic impairment, while patients with IBD represented a small minority of patients (5% of the overall population). The proportion of fulminant or life-threatening CDI was between 15% and 20%. These data are in accord with the results observed for severe CDI when applying the [ESMID, 2014] guidelines criteria where one-quarter of the CDI cases were considered to be severe.

The overall mortality in the ANEMONE population was 25.3%. Karas et al. [2010] identified 106 CDI cases admitted to Hinchingbrooke Hospital in UK between Oct 2006 and May 2008. The 30-day mortality among 66 CDI patients older than of 65 years was 37.9% (25 deaths), suggesting that the overall 30-day mortality was at least 23% (25/108). Lessa et al. [2015] performed an active surveillance across 10 geographic areas in the US in 2011. The death within 30 days after the diagnosis of CDI was 1.3% among incident, community-associated CDI patients and 9.3% among incident, health care-associated CDI patients. Lessa et al. intended to identify all incident CDI cases regardless of whether they were hospitalized or whether they had comorbidities. Different from the study by Lessa et al, subjects in ANEMONE were hospitalized patients (the duration of stay was 35 days on average and ranged from 1 to 253 days); 31.9% of the patients presented with severe CDI (according to the PI judgment).

Overall, there were no noteworthy detrimental effects of fidaxomicin treatment on the different laboratory parameters observed in the ANEMONE study population irrespective of the MCSI.

The proportion of clinically significant abnormal ECG results remained stable throughout the observation period although ECGs were administered in only a few patients.

The ANEMONE study population presented similar characteristics compared to other published retrospective studies assessing fidaxomicin in the treatment of CDI in real-world settings, notably in terms of demographics, methods for CDI confirmation, diarrhoea resolution rate and recurrence rate [Eiland et al, 2015; Shah et al, 2016; Goldenberg at al, 2016].

Conclusions

The ANEMONE study has characterised the use of fidaxomicin in a European population and has contributed to the requirements of the RMP by addressing specific safety concerns.

Almost half of the study population presented with at least 1 MCSI. IBD was the least represented condition while renal impairment of any severity and fulminant CDI-SS were the most common conditions. The observations related to laboratory assessments and ECGs did not indicate a safety concern for fidaxomicin treatment in patients with MCSIs.

The recommended dose regimen was followed by the vast majority of the study population and off-label use was observed in very few cases. For all MCSIs, a positive treatment response, as measured by resolution of diarrhoea, was observed.

In summary, the retrospective review of data collected in this DUS demonstrated compliance to Summary of Product Characteristics (SmPC) recommendations and did not reveal any particular safety concerns in the patients with an MCSI.

Marketing Authorisation Holder(s)

Astellas Pharma Europe BV

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