A Randomized, Placebo-controlled Trial of Fidaxomicin for Prophylaxis of Clostridium difficile-associated Diarrhea in Adults Undergoing Hematopoietic Stem Cell Transplantation

BACKGROUND:

- Patients undergoing hematopoietic stem cell transplants (HSCT) for a myriad of cancers are at a higher risk for the development of infectious *Clostridium difficile*-associated diarrhea (CDAD).
- Specifically, those undergoing auto-HSCT and allo-HSCT develop CDAD at rates of 5-15% and 12-34% during times of marked immunosuppression, respectively.
- Preventing occurrence of CDAD is an opportunity to curb the likelihood of complications such as graft-versus-host disease, bloodstream infections, and non-relapse mortality.

OBJECTIVE

- Determine efficacy and safety of prophylactic dosing of fidaxomicin to decrease incidence of confirmed CDAD in patients undergoing therapeutic HSCT.

METHODS

- **Design**: double-blind, placebo-controlled trial in patients undergoing therapeutic HSCT
- **Exclusion**: contraindication to oral treatment of confirmed CDAD, active or ongoing treatment for current CDAD, or patients taking medications with anti-CDAD activity for any other indication.
- **Inclusion**: >18 years old, undergoing HSCT, taking fluoroquinolone prophylaxis during neutropenia
- **Primary outcome**: composite endpoint of prophylactic failure defined as confirmed CDAD, receipt of CDAD effective medications for any reason, missing data (AE or death), missing data (any other reason) within 30 days of the last dose of fidaxomicin
- **Secondary outcome**: detection of prophylaxis failure at secondary timepoints of 60 days and 70 days post-prophylaxis
- **Sensitivity analysis**: confirmed CDAD at 30 and 60 days post-prophylaxis, and 70 days post-treatment initiation. Specific focus given to incidence in both auto- and allo-HSCT patients at 30 days and 60 days post-prophylaxis.
- 611 patients randomized, 600 patients received either
    - Fidaxomicin 250mg once daily (301 patients)
      OR
    - Equivalent placebo dose (299 patients)
- Power 90% with alpha level of 0.025 to detect a 6% difference in risk reduction between the 2 groups. Group sequential design was utilized, beginning with a target population of 340 subjects to achieve 90% power and detect a risk reduction of 0.06.
- Data handling method was modified intent-to-treat

RESULTS

- 64% of each treatment group completed the study (fidaxomicin n=194, placebo n=192)
- **Primary outcome measure:** There was no difference in prophylactic failure between fidaxomicin or placebo within 30 days post-prophylaxes. (mean difference 2.2%, p = 0.2778, 95% CI -5.1, 9.5)
- **Secondary outcome measure:** There was no difference in prophylactic failure between prophylaxes using fidaxomicin or placebo within 60 days post-prophylaxes (mean difference 0.6%, p = 0.4420, 95% CI -7.1, 8.2). There was no difference in prophylactic failure between fidaxomicin or placebo within 70 days post-treatment initiation (mean difference 1.9%, p = 0.3091, 95% CI 0.7, 15.8)
- **Sensitivity analysis:** There was a difference in incidence of confirmed CDAD between prophylaxes using fidaxomicin compared to placebo at the primary timepoint of 30 days post-prophylaxis (mean difference 6.4%, p = 0.0014, 95% CI 2.2, 10.6). A difference was observed in the auto-HSCT sample using fidaxomicin compared to placebo at the timepoint of 30 days post-prophylaxis (mean difference 5.1%, p = 0.0163, 95% CI 0.4, 9.8). A difference was observed in the allo-HSCT sample using fidaxomicin compared to placebo at the timepoint of 30 days post-prophylaxis (mean difference 8.2%, p = 0.0166, 95% CI 0.7, 15.8). There was a difference in incidence of confirmed CDAD between prophylaxes using fidaxomicin compared to placebo at the primary timepoint of 60 days post-prophylaxis (mean difference 5.1%, p = 0.0117, 95% CI 0.7, 9.4). A difference was observed in the auto-HSCT sample using fidaxomicin compare to placebo at the timepoint of 60 days post-prophylaxis (mean difference 4.5%, p = 0.0321, 95% CI -0.3, 9.4). A statistical difference was not observed in allo-HSCT patients at the 60 day timepoint. There was a difference in incidence of confirmed CDAD between prophylaxes using fidaxomicin compared to placebo at the primary timepoint of 70 days post-treatment initiation (mean difference 6.1%, p = 0.0026, 95% CI 1.8, 10.3).

STRENGTHS

- Double blind, placebo-controlled
- Blinding unlikely because side effect profile of fidaxomicin and placebo was comparable and difficult to distinguish from each other
- Sample size provided adequate power
- Choice of drug that yields high unlikelihood of drug interactions owing to its minimal systemic absorption
- Inclusion and exclusion criteria targeted a realistic patient population; these patients are likely to be found in real practice

- Dosing of drug was realistic and reproducible in practice

LIMITATIONS

- A prophylactic dosing regimen of fidaxomicin has not been previously studied. Once daily dosing was reported to have been sufficient to suppress *Clostridium difficile* within the gastrointestinal tract. It is difficult to apply pharmacokinetic parameters to establish a logical dose for a drug whose excretion is mostly dependent on the gut transit time.
- Inability to standardize the CDAD detection method among institutions
- Did not take into account the possibility of some patients taking antibiotic regimens with higher likelihoods of causing CDAD by decreasing other gut colonies
- Many authors have relationships with pharmaceutical companies who provided funds for any part of the study (Theravance Biopharma and Mylan). The potential for bias cannot be ruled out.

CONCLUSION

- Being a drug whose excretion is primarily based on a patient's individual gut motility, the task of establishing a pharmacokinetic-guided prophylactic dose of fidaxomicin that provides adequate suppression of target gut microbiota is difficult and murky.
- The cost burden of fidaxomicin may create an issue for hospitals supplying this drug to the patient.
- Vancomycin is a cheaper medication that is effective for treatment of CDAD. Although higher rates of recurrence of CDAD are attributed to vancomycin compared to fidaxomicin, the cost-benefit would likely be worth it when considering the monetary difference in supplying the drug to the patient.
- Without regards to cost benefit, the data from this study can be extrapolated to the targeted patient population. The findings are clinically significant when applied to a population of patients who are similar to the sample of patients in this study.

FUTURE RESEARCH

- Since fidaxomicin has been established as non-inferior to vancomycin (a less expensive drug) in the treatment of CDAD, vancomycin prophylaxis should be explored if the need for such prophylaxis in this patient population is truly needed.
- Experiment with more frequent dosing regimens in patients who are colonized with *C. diff*, while maintaining the once daily dosing in patients who are not colonized.
- Further follow-up with patients from this study to determine if the incidence of graft-versus-host disease, bloodstream infections, and non-relapse mortality a year after the cessation of prophylactic dosing would help determine if using fidaxomicin for this indication truly prevents negative outcomes associated with CDAD.

Mullane KM, Winston DJ, Nooka A, et al. A Randomized, Placebo-controlled Trial of Fidaxomicin for Prophylaxis of Clostridium difficile-associated Diarrhea in Adults Undergoing Hematopoietic Stem Cell Transplantation. Clin Infect Dis. Jan 2019;68(1):106-203.

Shelby Anderson, Doctor of Pharmacy Candidate