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Fidaxomicin vs. pulsed, tapered vancomycin for treatment of recurrent *C. difficile*-associated diarrhea: a prospective, randomized, double-blind, multicenter clinical trial

A. Study Purpose and Rationale

Clostridium difficile-associated diarrhea (CDAD) is a serious infection that occurs in up to 20% of hospitalized patients.[1] It is caused by the bacterium *Clostridium difficile,* a gram positive rod that produces toxins responsible for clinical disease. Symptoms range from mild abdominal pain with diarrhea to pseudomembranous colitis and life-threatening fulminant toxic megacolon. In its dormant state, *C. difficile* produces spores which are extremely resistant to most traditional methods of destruction and can be present on surfaces for months to years.[2] The spores are largely responsible for the epidemic infections that can occur in the healthcare setting, as they are readily transmissible in the absence of proper handwashing and infectious precautions. Up to 50% of hospitalized patients are colonized with virulent strains of *C. difficile*, whereas only 2-3% of healthy individuals are colonized.[1] In the setting of antibiotic usage, the normal colonic flora is disrupted and in colonized individuals, *C. difficile* infection results.

Fidaxomicin is a new drug approved by the FDA in 2011 for the treatment of *Clostridium difficile* associated diarrhea.[3] It belongs to the category of drugs called macrocylics, referring to the drugs' multi-ring structure, and works by inhibiting protein synthesis and ultimately causing cell death.[4] Its bactericidal mechanism of action distinguishes it from all other currently available treatments for *C. difficile* diarrhea. Additionally, fidaxomycin's limited spectrum of activity makes it specific for *C. difficile* and leaves the rest of the colonic flora intact. This is thought to play a major role in its effectiveness and patients' rapid time to recovery.[5]

Fidaxomicin has been shown to be non-inferior to vancomycin for the treatment of CDAD during the first episode or the first recurrence after treatment.[5] However, little data exists regarding the optimal treatment of CDAD after two or more recurrences. It is estimated that 20-35% of patients have recurrence of CDAD after completion of an initial course of antibiotics, and many of these individuals go on to have repeat occurrences lasting for months and even years.[6] The mechanism of recurrence is either from relapse, due to persistent spores in the colonic mucosa, or from reinfection with a different strain of *C. difficile*. There is a paucity of data on the appropriate management of these patients, who usually have significant medical comorbidities and are often receiving antibiotics for other, unrelated infections.[7,8] One strategy for treating recurrent *C. difficile*-associated diarrhea is to use vancomycin in a pulsed, tapered fashion.[9]

The healthcare burden associated with *C. difficile* infection is substantial. With the emergence of a particularly virulent strain of *C. difficile*, BI/NAP1/027 and an increase in the morbidity and mortality associated with CDAD overall,[1] new guidelines for management are essential. Fidaxomicin could represent a novel intervention broadly applicable to many patient populations, including those with recurrent CDAD.

B. Study design and statistical analysis

This study will compare fidaxomicin to pulsed and tapered vancomycin in patients with two or more recurrences of CDAD. It will be a prospective, multicenter, double-blind, randomized, parallel group trial. Approximately 604 patients will be enrolled, with 302 in each group, to detect a 10% difference between fidaxomicin and vancomycin with 80% power. Participants will be stratified according to whether this is their 2nd recurrence or greater than their second recurrence of CDAD and randomly assigned to fidaxomicin or pulsed, tapered vancomycin for the duration of the study. No cross-over will occur.

Subjects will receive the study medication orally each day for 6 weeks (42 days). Vancomycin dosing will be along a tapered regimen as follows: 125 mg orally four times daily for 7 days, 125 mg orally twice daily for 7 days, 125 mg orally once daily for 7 days, 125 mg orally every other day for 7 days, and 125 mg orally every 3 days for 14 days. Dosing for fidaxomicin will be 200mg every 12 hours for 10 days with matched doses of placebo.

CDAD will be defined as the presence of diarrhea (a change in bowel habits, with more than three unformed bowel movements or >200mL unformed stool for subjects with rectal collection devices in the 24-hour period before randomization) and *C. difficile* toxin A, B, or both in a stool specimen obtained 48 hours before randomization. Clinical cure will be defined as resolution of diarrhea with no further requirement for therapy for *C. difficile* infection as of the second day after the course of therapy. Clinical failure will be defined as persistent diarrhea after completing a full course (42 days) of pulsed, tapered vancomycin therapy. Clinical recurrence will be defined by the reappearance of more than three diarrheal stools per 24-hour period within 90 days after the cessation of therapy; *C. difficile* toxin A or B, or both, in stool; or a need for treatment for *C. difficile* infection. Global cure will be defined as the resolution of diarrhea without recurrence.

Patients will be assessed daily for clinical cure or failure during the 42-day course of therapy. If a patient meets the criteria for clinical cure at any time during the course of therapy, the patient will be followed for recurrence by means of a weekly assessment and at day 90 following treatment. If the patient notes recurrence of diarrhea after clinical cure has been declared, reassessment by the study team with *C. difficile* detection and restriction-endonuclease typing in stool will ensue.

C. difficile detection in stool will be accomplished through the use of cytotoxin assays. The primary outcome will be the global cure rate in the intention to treat analysis. The secondary outcome will be time to resolution of diarrhea, measured in days from the start of treatment until the day when the criteria for clinical cure are met. Statistical analysis will be performed by means of a chi-squared test for primary outcome, in which the categorical outcome of presence or absence of global cure will be assessed at a significance level of $p = 0.05$. Kaplan-Meier analysis will be used for secondary outcome with Wilcoxon comparison of curves at the same significance level.

C. Study Procedure

Stool samples will be analyzed by means of cytotoxin assay tests. These tests are considered the gold standard in the detection of *C. difficile* in stool samples. In the laboratory, the stool sample being evaluated is diluted in solution and applied to a thin layer of epithelial cells. The toxins produced by *C. difficile* have a toxic effect on the cells, causing them to round up. After the stool has been applied. the epithelial cells are then incubated overnight, and are evaluated at 24 and 48 hours. *C. difficile* is confirmed when an antitoxin reverses the effects of

the toxin on the cells and causes their shape to return to normal.[2]

Fecal samples for toxin assays to verify *C. difficile* infection will be collected at the time of screening and enrollment, at the time of early termination in the case of patients with clinical failure (persistent diarrhea upon completion of 42-day course of therapy or recurrence of diarrhea before the interval end point), and at follow-up assessment for recurrence at day 90 after treatment. The study participants should experience no discomfort or inconvenience from the collection of these stool samples. Restriction-endonuclease typing will be performed on all stool samples to evaluate the strain of *C. difficile* initially and, in the event of treatment failure, to determine if relapse or reinfection has occurred

After enrollment, participation in the study will last for 132 days and will be terminated when the final fecal specimen has been analyzed. It is expected that it will take approximately one year to enroll an adequate number of participants in the study to generate meaningful data.

D. Study Drugs

This study will evaluate fidaxomycin, a drug approved by the FDA in 2011 for the treatment of *C. difficile*-associated diarrhea. Fidaxomycin was demonstrated to be non-inferior to vancomycin for patients treated during the first incidence of CDAD or the first recurrence after treatment[1]. Fidaxomicin is administered orally and is safe and well-tolerated. It is taken as 200mg capsules two times per day for 10 days.[4] For this study, fidaxomicin will be administered according to the standard regimen. It has little systemic absorption, as its action is largely confined to the gastrointestinal tract. Serum concentrations after administration of fidaxomicin have been minimal to undetectable. More than 92% of fidaxomicin and its active metabolite are excreted in the stool.[4] Common adverse effects include nausea (11%), and in rarer cases, gastrointestinal hemorrhage, vomiting, and abdominal pain (4%); anemia and neutropenia (2%), as well as abdominal distension, abdominal tenderness, alkaline phosphatase increased, blood bicarbonate decreased, drug eruption, dyspepsia, dysphagia, flatulence, hepatic enzymes increased, hyperglycemia, intestinal obstruction, megacolon, metabolic acidosis, platelet count decreased, pruritus, rash (<2%).[4]

E. Medical Devices

Not applicable.

F. Study Questionnaire

Not applicable.

G. Study Subjects

Subjects will be eligible for the study if they are 18 years or older with a diagnosis of *C. difficile* infection, defined by the presence of diarrhea (a change in bowel habits, with more than three unformed bowel movements or >200mL unformed stool for subjects with rectal collection devices in the 24-hour period before randomization) and *C. difficile* toxin A, B, or both in a stool specimen obtained within 48 hours before randomization. Subjects must also have failed standard treatment for *C. difficile* infection with either metronidazole or vancomycin (according

to standard dosage guidelines) at least two times in the four months before randomization. Patients were excluded if they had life-threatening or fulminant *C. difficile* infection, toxic megacolon, previous exposure to fidaxomicin, a history of ulcerative colitis or Crohn's disease, or had been treated with any therapy for *C. difficile* other than metronidazole or vancomycin.

H. Recruitment of Subjects

Subjects will be recruited for the study during their hospitalization once the diagnosis of *C. difficile* infection has been made, according to the definitions outlined above.

I . Confidentiality of Study Data

Upon randomization, all participants in the study will receive a unique study code number. Personal identifying information, including hospital unit numbers, social security numbers, subject names/initials, phone numbers, and addresses will be removed. The information used in the study will be stored in a secure database, accessible only to the investigators.

J. Conflict of Interest

None of the investigators have a proprietary interest in fidaxomicin or any of the drugs used in this investigation. There is no conflict of interest to disclose.

K. Location of the Study

This is a multi-center study that has been reviewed and approved by the IRB at each of the participating centers.

L. Potential Risks

Although there is the risk that fidaxomicin may not be as effective as pulsed, tapered vancomycin for the treatment of two or more recurrences of CDAD, the investigators do not believe that this will be the case given the available data. However unlikely, though, the subjects who receive fidaxomicin may clinically worsen.

M. Potential Benefits

You may or may not benefit from your participation in this study. It is possible that by taking fidaxomicin, your condition may improve. Even if you do not directly benefit from fidaxomicin, your participation in this study will help other patients by providing new information about fidaxomicin and its effectiveness.

N. Alternative Therapies

Other antibiotics such as rifaximin are sometimes used in conjunction with vancomycin for refractory *C. difficile* infection. Although this has been demonstrated to be effective in some

cases, there is a serious concern that because some individuals have been previously exposed to rifamicins, the continued use of rifaximin for *C. difficile* infection will promote the development of antibiotic-resistant bacteria.[9] Another therapy, fecal floral reconstitution, involves transfer of stool from healthy subjects to patients with recurrent, refractory CDAD. Although this has demonstrated some small efficacy in the literature, this treatment is performed over the course of five years and needs to be further study before its true efficacy can be determined.[11] Probiotics have sometimes been used to help with the recovery from *C. difficile* infection, but data regarding their use has been inconclusive.[12] Monoclonal antibodies against toxins A and B produced by *C. difficile* are being developed but are not yet currently available.[13]

O. Compensation to Subjects

No compensation to subjects participating in this study will be provided.

P. Costs to Subjects

The subjects will not incur any additional costs as a result of participating in this study.

Q. Minors as Research Subjects

Not applicable.

R. Radiation or Radioactive Substances

Not applicable.

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