The efficacy, safety and tolerability of tegaserod in celiac disease patients

A. Study Purpose and Rationale:

Celiac disease is an autoimmune inflammatory disease of the small intestine induced by the ingestion of gluten, the storage protein of wheat, barley, and rye. Patients can present in a variety of obvious and occult ways, but usually present with diarrhea, abdominal pain, bloating, and signs of malabsorption, such as weight loss and anemia.[1] These symptoms usually resolve after elimination of gluten from the diet—however, there are patients on a gluten-free diet whose symptoms do not improve.

There are consistent data available on the presence of disturbed motility of the esophagus[2], stomach[3], small intestine[4], gallbladder[5], and colon[6] of celiac disease patients. More specifically, esophageal transit, gastric and gallbladder emptying, and orocecal transit time are delayed, while colonic transit is faster.[7] Studies show that the motility effects in the small intestine are more potent than in the colon.[4-7] The most common hypotheses for the etiology of this disturbance include: a neurohormonal factor[8], reduced absorption of food constituents such as starch and fat, and severe inflammation of the mucosa, especially in the small intestine.[7]

Tegaserod maleate (Zelnorm®), a 5-HT_4 (5-hydroxytryptamine or serotonin) receptor partial agonist, has been shown to accelerate gut transit from the oral cavity to the colon.[9,10,11] This acceleration in transit time has been shown to correlate with improvement in symptoms of irritable bowel syndrome[12,13,14] and chronic idiopathic constipation.[15] This drug has not been studied in celiac disease patients, but it is assumed that tegaserod will also accelerate intestinal transit time in these patients, and thus possibly improve symptoms such as abdominal pain and bloating in patients whose symptoms do not improve on a gluten-free diet. However, there is reason to believe that the drug may have more adverse than beneficial effects—as discussed above, patients with celiac disease have been shown to have more rapid colonic transit. Since tegaserod has been shown to accelerate motility throughout the gastrointestinal tract, there is the possibility that the proposed treatment could actually worsen their symptoms by exacerbating their diarrhea. But we also know that tegaserod increases small intestinal motility more than colonic motility, so there may ultimately be no difference in outcomes in celiac disease patients. Thus, our goal is to determine whether tegaserod maleate will safely improve gastrointestinal symptoms in celiac disease patients whose symptoms do not respond to a gluten-free diet and who have delayed small intestinal transit times.

B. Study Design and Statistical Analysis:

This study will be performed as a randomized, placebo-controlled, double-masked study. Subjects will be recruited from a database of celiac disease patients at the Celiac Disease Center of the Columbia University Medical Center. Only those patients whose symptoms are refractory to a gluten-free diet and have delayed small intestinal transit time on lactulose hydrogen breath test will be considered for the study. Subjects will be randomized to a 4-week course of either tegaserod 6 mg twice a day (the dose approved by the FDA for the treatment of constipation-predominant irritable bowel syndrome and idiopathic chronic constipation) or a matching placebo. Symptoms will be assessed by a questionnaire using 100 mm visual analogue scales, quantifying the severity and/or

frequency of each symptom. The questionnaire has been modeled after questionnaires that have been proven to be validated instruments in assessing symptoms in functional gastrointestinal disorders.[16] Intestinal transit time will be measured by lactulose hydrogen breath test. Adverse effects will be evaluated by an open-ended question. There will be two primary outcomes: improvement or worsening in severity or frequency of abdominal pain and diarrhea. Secondary outcomes will include: improvement or worsening in severity of frequency of overall symptoms of celiac disease, bloating, and small intestinal transit time.

Our results will be analyzed using an unpaired t-test, as there are two parallel groups and continuous variables being compared. Based on the principal investigator's prior knowledge of how many patients at the Celiac Disease Center may meet criteria and be enrolled in the study, and assuming a withdrawal rate of about 10%, 20 patients will be enrolled in each arm of the study. Assuming a power of 80% and a p-value of 0.05, we will be able to detect an effect size roughly equal to the standard deviation. There are no published results on the mean and associated standard deviation of the improvement of symptoms as a continuous variable with the use of tegaserod in patients with other gastrointestinal disorders. Most of the other studies have dichotomous results (e.g. Did the patient's abdominal pain "respond" to the treatment? Yes or no?), and thus have non-applicable results. However, there are published means and standard deviations on the effect of tegaserod on transit time. Using an unpaired t-test and previously published data from Degen et al (2005) giving the mean difference in transit time between tegaserod and placebo and the associated standard error of the mean, we calculated that each study group should have a sample size of 20 to be effectively powered.

C. Study Procedure:

After patients have been recruited, meet inclusion and exclusion criteria (as specified below), and sign an informed consent form, they will be randomized to a 4-week course of gluten-free tegaserod maleate or matching placebo. The study will consist of two separate clinic visits—one before treatment and one afterwards—where they will complete a symptom questionnaire and perform a lactulose hydrogen breath test, which is the test that will be used to determine small intestinal transit time. Between these two visits, there will be communication between the subject and the study coordinator by phone and fax on 3 different occasions, each involving a study questionnaire.

Before the subjects' first visit, instructions will be mailed regarding special foods that should be avoided for 24 hours before the visit. The subject will also be instructed not to eat anything starting 12 hours before his/her appointment.

At the initial visit, a baseline symptom questionnaire will be completed (see below for questionnaire), as well as a baseline lactulose hydrogen breath test. Bacteria, normally only in the large intestine, produce hydrogen through the fermentation of sugars (e.g. the lactulose used in this particular study). In the hydrogen breath test, the concentration of hydrogen will be measured at regular intervals to determine the amount of time it takes for the hydrogen concentration to suddenly peak, which is the time when lactulose has reached the large intestine, which is filled with bacteria. For the test, the subject drinks 20 grams of lactulose, and then blows into a straw connected to a hydrogen detector every 20 minutes to determine the concentration of hydrogen in parts per

million. Usually after about 60 minutes, the hydrogen concentration will start to rapidly increase—this is the point when the lactulose has reached an area of more bacteria, which should be the colon in normal subjects (meaning those people who do not have small intestinal bacterial overgrowth and thus have high hydrogen concentrations on hydrogen breath test when the lactulose is still in the small intestine). Those subjects with hydrogen peaks later than 100 minutes are considered to have "delayed intestinal transit". Breath measurements will be made every 20 minutes until the peak and plateau of hydrogen concentration are recorded, or until 360 minutes, whichever comes first.

The subjects will then be sent home with a 4-week supply of tegaserod or matching placebo in a pillbox. At the end of every week, they will complete a symptom questionnaire (consisting of the same questions as the baseline symptom questionnaire) and fax it to the Celiac Disease Center. If the questionnaire is not received 2 days after it is due, a follow-up phone call will be made by a study coordinator (not a physician) to remind the subject. A total of 3 questionnaires for 3 weeks will be received by fax. After 4 weeks of treatment, the subject will return for the second study visit, where a final questionnaire will be completed and a post-treatment lactulose hydrogen breath test will be performed. The same instructions given to the subject before the first breath test will again be mailed to the subject before the second breath test.

D. Study Drug (see Investigator's Brochure below):

Tegaserod maleate is a 5-HT_4 receptor partial agonist, approved by the FDA for treatment use in females with constipation-predominant irritable bowel syndrome and in adults younger than 65 years of age with chronic idiopathic constipation. It has been shown to accelerate gut transit time from the stomach to the colon in patients with delayed intestinal motility[8,9,10] and also improve symptoms of constipation and bloating[11,12,13]. Tegaserod is usually given 6 mg orally twice a day before meals, which is the dose, method and route of administration that will be used in this study. Common side effects include: headache (15%), diarrhea (9%), dizziness (4%). Rare, but serious, side effects include: severe diarrhea (0.04%) requiring IV rehydration, hypotension, hypovolemia and syncope. There are also case reports of angina, arrhythmia, bundle branch block and supraventricular tachycardia associated with tegaserod therapy, but not necessarily caused by the drug; as well as ischemic colitis, cholecystitis with elevated liver enzymes and bile duct stones.[17]

E. Medical Device: not applicable

F. Study Questionnaires: See attached questionnaires.

G. Study Subjects:

Inclusion criteria:

- Men and women
- Ages 18-65
- Celiac disease proven by small intestinal biopsy (total villous atrophy, partial villous atrophy, crypt hyperplasia with lymphocytosis)
- Symptoms associated with celiac disease refractory to a gluten-free diet

- Delayed small intestinal transit time on lactulose hydrogen breath test (delayed hydrogen concentration peak after 100 minutes)

Exclusion criteria:

- Active use of prokinetic (e.g. laxatives) or antimotility (e.g. loperamide) agents (subjects can participate in study if they discontinue use of medication at least one week prior to initial questionnaire)
- Use of antidepressants
- Severe hepatic impairment
- Severe renal impairment
- Co-morbid conditions that affect motility (e.g. diabetes, Parkinson's disease)
- Abdominal surgery other than appendectomy
- Known bowel adhesions
- Pregnancy or breast-feeding
- Inability to give informed consent

H. Recruitment of Subjects: Subjects will be recruited by letter or telephone on the recommendation of one of the celiac disease specialists (Dr. Peter Green, Dr. Suzanne Lewis, Dr. Susie Lee) at the Celiac Disease Center. See attached recruitment letter and telephone script.

I. Confidentiality of Study Data: After patients are recruited and agree to participate in the study, they will be identified in all study records by a unique personal identification number, not related to their name, birthday, phone number, address, social security number, or medical record number. Only the principal investigator, co-investigator, and study coordinator will have access to the subjects' information, which will be stored in a computer only accessible by password by those three named individuals.

J. Potential Conflict of Interest: There is no known potential conflict of interest applicable to any of the investigators. Funding will be requested from Novartis (makers of Zelnorm®). However, if funding is provided, the study medication and placebo will be re-packaged at the Columbia Research Pharmacy, and the company will not participate in the study in any other roles.

K. Location of the Study: The study will take place at the principal investigator's department, the Celiac Disease Center of the Columbia University Medical Center (Harkness Pavilion, 180 Fort Washington Avenue, Suite 934, New York, NY 10032).

L. Potential Risks:

- Hypersensitivity reaction to study drug
- May receive placebo instead of active treatment (in the case that treatment is beneficial)
- Treatment may cause profuse diarrhea, severe enough to cause dehydration requiring IV fluids or syncope
- Other adverse effects associated with tegaserod may occur (most common ones including diarrhea, headache and dizziness)

- Have to be NPO starting at midnight the night before each visit and stay up to 6-7 hours at each visit, performing a lactulose hydrogen breath test

M. Potential Benefits:

- Improvement in symptoms associated with celiac disease
- Further insight into mechanism behind delayed gastrointestinal transit in celiac disease patients
- Determine if tegaserod can safely be used in patients with celiac disease

N. Alternative Therapies: There are no alternative therapies approved by the FDA for celiac disease patients with symptoms related to delayed small intestinal transit time.

O. Compensation to Subjects: Subjects will be monetarily compensated (amount to be determined after amount of funding by Novartis is determined). Payment will be in the form of cash, to be given in 2 installments, the first after the initial visit, the second after the final visit. The first payment will be 25% of the total payment, and the remaining 75% will be given after the subject satisfactorily completes the remaining questionnaires and comes to the final visit.

P. Costs to Subjects: There are no costs to the subjects involved with the study, except for possible loss of work-time at initial and follow-up visits. Parking at the hospital will be reimbursed.

Q. Minors as Research Subjects: not applicable

R. Radiation or Radioactive Subjects: not applicable

Investigator's Brochure
tegaserod maleate

Mechanism of Action

- 5-HT_4 receptor partial agonist
- binds with high affinity
- activation of receptors increases peristaltic reflex, intestinal secretion, and releases neurotransmitters such as calcitonin-gene related peptide from sensory neurons

Previous Clinical Trials

1. Prather CM et al., Tegaserod Accelerates Orocecal Transit in Patients with Constipation-Predominant Irritable Bowel Syndrome, Gastroenterol (2000);118:463-468.
   - Tegaserod accelerates orocecal transit and tends to accelerate colonic transit.

2. Degen L et al., Tegaserod, a 5-HT_4 receptor partial agonist, accelerates gastric emptying and gastrointestinal transit in healthy male subjects, Aliment Pharmacol Ther (2001);15:1745-1751.
   - In healthy subjects, tegaserod markedly accelerated gastric emptying and small intestinal transit, and induced a small, but significant acceleration of colonic transit. Tegaserod can act as a promotile agent throughout the gastrointestinal tract.

3. Muller-Lissner S, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT_4 receptor partial agonist relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther. 2001;15:1655-1666.
   - Tegaserod offers rapid and sustained relief of the abdominal pain and constipation associated with irritable bowel syndrome, and is also well tolerated.

4. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2002;16:1877-1888.
   - Tegaserod produced rapid and sustained improvement of symptoms in female irritable bowel syndrome patients and was well tolerated.

5. Degen L et al., Effect of tegaserod on gut transit in male and female subjects, Neurogastroenterol Motil (2005);17:821-826.
   - In both healthy male and female subjects, tegaserod markedly accelerated small intestinal transit, and induced a significant increase in gastric emptying time and colonic transit. Results imply that tegaserod is a potent prokinetic agent throughout the gastrointestinal system in both sexes.

6. Tack J, Muller-Lissner S, Bytzer P, et al. A randomized controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. Gut. 2005;54:1707-1713.
   - Tegaserod provides rapid and sustained relief of IBS-C symptoms both during first and repeated treatment.

7. Kamm MA, Muller-Lissner S, Talley NJ, et al. Tegaserod for the Treatment of Chronic Constipation: A Randomized, Double-Blind, Placebo-Controlled Multinational Study. Am J Gastroenterol. 2005;100:362-372.

- Tegaserod was efficacious in relieving symptoms of chronic constipation and was well tolerated

Pharmacological Information

- comes in oral tablets of 2 mg or 6 mg each
- usual dose in treatment is 6 mg orally, twice-a-day, before meals
- time to peak concentration is approximately 1 hour
- bioavailability is approximately 10% (food reduces bioavailability by 40-65%)
- metabolized in the intestine and liver, excreted renally (33%) and through feces (66%)
- elimination half-life is 11 +/- 5 hours

Adverse Effects

1. Common adverse effects
   - gastrointestinal: diarrhea (9%)
   - neurologic: headache (15%), dizziness (4%)

2. Rare, but serious adverse effects
   - cardiovascular: hypotension, hypovolemia, syncope
   - gastrointestinal: severe diarrhea (0.04%), cholecystitis with transaminitis, bile duct stones

Symptom Questionnaire

1. **Abdominal Pain:** On a scale of 0-100, 0 being no pain and 100 being the most pain you have ever experienced, how severe or frequent was your abdominal pain over the past 7 days? Please mark an X on the line below.

0_____100

2. **Diarrhea:** On a scale of 0-100, 0 being no diarrhea and 100 being the most frequent or severe diarrhea you have ever experienced, how severe or frequent was your diarrhea over the past 7 days? Please mark an X on the line below.

0_____100

3. **Bloating**: On a scale of 0-100, 0 being no bloating and 100 being the most severe bloating you have ever experience, how severe or frequent was your bloating over the past 7 days? Please mark an X on the line below.

0_____100

4. **Overall celiac disease symptoms**: On a scale of 0-100, 0 being no symptoms and 100 being the most severe symptoms you associate with celiac disease, how severe or frequent were your overall symptoms over the past 7 days? Please mark an X on the line below.

0_____100

Recruitment Letter

Peter Green, MD
Elizabeth Hwang, MD
Celiac Disease Center
180 Fort Washington Avenue
Suite 934
New York, NY 10032

Subject Name
Subject Address

Date

Dear **Subject Name**,

As a patient at the Celiac Disease Center at Columbia University Medical Center, you have been recommended to us by your doctor, _____, as a possible participant for a research study we are doing with Zelnorm, a drug that is being used to treat patients with other stomach and intestinal disorders, like irritable bowel syndrome. Your doctor specifically recommended you to us because you have symptoms that are not improving on a gluten-free diet. If you would like more information about the study, please call 212-342-4529 or e-mail celiacstudy@gmail.com. You do not have to join the study if you ask for more information. Thank you for your time and consideration in helping us learn more about celiac disease.

Sincerely,

Peter Green, MD and Elizabeth Hwang, MD

Recruitment Telephone Script

May I please speak to **Subject Name**?

Hello, my name is _____, and I am calling from the Celiac Disease Center at the Columbia University Medical Center. Your doctor, _____, recommended you to us as a possible participant in a research study we are doing with Zelnorm, which is a drug that is being used to treat patients with other stomach and intestinal disorders, like irritable bowel syndrome. Your doctor specifically recommended you to us because your symptoms have not been improving on a gluten-free diet.

Would you like more information on the research study? You do not have to join the study if ask for more information.

References

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