IRB Proposal:
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A. Study Purpose and Rationale

Diarrhea is a common side effect of numerous medications; however, a severe form of chronic diarrhea that is associated with the use of olmesartan has recently been described in a series of case reports.[4] Individuals taking olmesartan developed a chronic severe diarrhea that on biopsy showed villous atrophy resembling that found in celiac disease. However, these individuals lacked diagnostic markers of celiac disease (e.g. IgA tissue transglutaminase antibodies) and derived no clinical improvement from a gluten-free diet. Significant clinical and histological response resulted, however, after the termination olmesartan of use.

Olmesartan is an angiotensin II receptor-blocker (ARB) commonly prescribed for the treatment of hypertension. The primary use of olmesartan is for controlling blood pressure, with particular indication for its use in individuals who also have diabetes, chronic kidney disease or heart failure. There are several other ARBs that are also prescribed for the same indications, although olmesartan is the only member of this class that has been associated with severe chronic diarrhea thus far, although other studies are investigating chronic diarrhea with other ARBs as well.

A class of medications related to ARBs is the angiotensin-converting enzyme (ACE) inhibitors, which function on the same pathway as ARBs although at a separate point. ARBs act at the angiotensin II receptor whereas ACE inhibitors work upstream on the enzyme that produces angiotensin II. The indication for the use of ACE inhibitors is the same as that of ARBs, namely in the control of blood pressure, with particular emphasis for their use in those with co-morbid diabetes, chronic kidney disease or heart failure. Both ACE inhibitors and ARBs are generally well tolerated, although it is common practice to start ACE inhibitors preferentially to ARBs.[1] This preference results from the fact that ACE inhibitors, as a class of medications, pre-date ARBs and many studies establishing the benefit of use in particular populations e.g. diabetics, were first shown with the use of ACE inhibitors. [3]

A driving force behind the development of ARBs was to produce a more precise target than ACE inhibitors on the renin-angiotensin pathway. For instance, cough is a common and well-recognized side effect of ACE inhibitors (average 9.9% prevalence) that leads to the need for discontinuation of the drug or transition to ARBs, which so far appear to have a much better tolerated side effect profile than ACE inhibitors.[2] The association between olmesartan (and other ARBS) and chronic diarrhea, however, may represent a newly recognized limitation to the sole use of ARBs. There have been studies comparing ACE inhibitors and ARBs in the past, but none has looked at the incidence of severe diarrhea in particular. We hypothesize that there will be a significant increase in the incidence of chronic diarrhea among individuals who are started on an ARB (i.e. olmesartan).

B. Study Design and Statistical Analysis

The design of the study is a two-arm randomized controlled trial. A total of 1000 subjects over 50 years of age in the outpatient setting who have been on lisinopril for at least 90 days will be randomized into one of the two groups: those continuing lisinopril versus those switching to olmesartan. Randomization will occur when subjects present for their appointment, where their physician will receive from the investigators an envelope containing a prescription for either

lisinopril or olmesartan. Participants will be followed for 12 months on these medications during which time they will be questioned about side effects related to their medication use at 3-month intervals, with particular emphasis on quantifying the amount of diarrhea if this is reported as a side effect. The primary outcome will be development of chronic (> 4 weeks) diarrhea. With at least 428 patients in each arm, we will have 80% power to detect a difference between two groups with $p < 0.05$ using chi square test (see below power analysis):
n = $[8(p1q1 + p2q2)/effect^2]$ + 2/effect + 2 = **428**
p1 = 0.025 q1 = 0.975
p2 = 0.001 q2 = 0.999
effect = 0.024

C. Study Procedure.
No procedures will be performed.

D. Study Drugs
Both lisinopril and olmesartan are FDA-approved and readily available medications and will be used for their approved indications in this study.

E. Medical Device.
No medical devices will be used.

F. Study Questionnaires
Participants will receive a questionnaire at their appointments at 3-month intervals that asks them to identify any side effects they perceive as resulting from their use of lisinopril or olmesartan.

G. Study Subjects
Exclusion criteria would be chronic diarrhea (>4 weeks) prior to study including conditions, such as inflammatory bowel disease and celiac disease, as well as any previously diagnosed olmesartan associated diarrhea. Those also taking an ARB at the time of randomization will also be excluded.

H. Recruitment of Subjects
Individuals in any of the CUMC outpatient clinics (e.g. AIM, ACN) who meet the study requirements will be eligible for enrollment. Researchers contact providers regarding opening of enrollment of the study and post flyers for reminders at each clinic site.

I. Confidentiality of Study Data
Patient information will be kept under password protection that is accessible to the researchers alone.

J. Potential Conflict of Interest
None

K. Location of the Study
CUMC

L. Potential Risks
Developing serious adverse effect from the medications in question could result in hospitalization e.g. for severe spruelike enteropathy. No reports of death from this cause have been reported.

M. Potential Benefits
Awareness of a significant side effect that may limit reliance on the long-term use of olmesartan or other ARBs in a subset of patients. A negative study would also be important to exclude the risk of this side effect in an increasingly-popular class of medications.

N. Alternative Therapies
All patients in the study will have an indication for continuance on

0. Compensation to Subjects
No compensation will be provided to participants.

P. Costs to Subjects
No cost to subjects.

Q. Minors as Research Subjects
No minors.

R. Radiation or Radioactive Substances
No radiation.

References

1. Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000; 355:637.
2. Kaplan NM. Major side effects of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. In: UpToDate, Bakris GL, Forman JP (Ed). UpToDate, Waltham, MA, 2013.
3. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358:1547.
4. Tapia AR, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT, Murray JM. Severe Spruelike Enteropathy Associated with Olmesartan. *Mayo Clinic Proc* 2012; 87:732-738.