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IRB Proposal
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Randomized, double masked study using lipoic acid as a supplement to standard of care treatment for Alzheimer's disease

A. Study Purpose and Rationale

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is characterized by progressive memory loss and ultimately leads to dementia. The pathological hallmarks include: synapse loss, extracelluar senile plaques, and intracellular neurofibrillary tangles. One in eight older Americans has this disease and it is currently the sixth leading cause of death in the USA. In 2012, payments for care were estimated to be $200 billion. (Alz Org, 2012)

Alzheimer's disease and Diabetes Type II

Recently, several studies have investigated the association between diabetes type 2 and hyperinsulinemia and the risk of Alzheimer's disease. Although there has been some preliminary conflicting evidence over whether T2DM or glucose intolerance is the condition that affects AD and cognition, there is a strong association between the two diseases. Diabetes is a risk factor for dementia. Elevated glucose levels may even be a risk factor for dementia in people without diabetes (Crane, 2013). Hypotheses of how glucose intolerance negatively affects the brain range from the induction of oxidative stress to glycosylation of key regulatory proteins (Yan, 1997; Sasaki, 2001). Another association has been reported that brain insulin degrading enzyme (IDE) regulates the metabolism of insulin and the deposition of amyloid beta. As peripheral insulin crosses the blood brain barrier, the insulin competitively inhibits IDE and impairs the metabolism of amyloid beta leading to amyloid deposition (Farris, 2003). Insulin receptors have also been found in the dentate gyrus and the CA1 subfield of the hippocampus, the structure affected first in AD (Small, 2002). In a different study, hyperinsulinemia and not DM, had a higher risk of AD and was also related to a significant decline in memory-related cognitive scores (Luchsinger, 2004). Both AD and T2DM have comparable pathological features that involve amyloid deposition. In a study done in 2004, autopsy cases were examined and investigators found that islet amyloid was more frequent and extensive in patients with AD vs. control patients (Janson). Even though diffuse and neuritic plaques were not more commonly found in T2DM, when these plaques were present the density of the plaques correlated with the duration of the T2DM and not with age (Janson, 2004).

Alzheimer's disease, Diabetes Type II, and Alpha-lipoic acid

Lipoic acid (LA) is a naturally occurring cofactor for mitochondrial enzymes pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase. The biologically active R-(+)-alpha lipoic acid has been found in vitro to enhance glucose uptake in skeletal muscle and adipocytes and to increase glucose utilization in vivo (Estrada, 1996; Seaton, 1996). This cofactor has been shown to have many properties that would allow it to interfere with the pathogenesis and progression of AD. Briefly, it has been suggested that LA may affect AD in these ways: "A) To increase acetylcholine production by activation of choline acetyltransferase, B) To increase glucose uptake, supplying more acetyl-CoA for the production for acetylcholine, C) To chelate redox-active transition metals, inhibiting the formation of hydrogen peroxide and hydroxyl

radicals, D) To scavenge reactive oxygen species (ROS), increasing the level of reduced glutathione, E) To scavenge reactive oxygen species (ROS), down-regulating inflammatory processes, F) To scavenge lipid peroxidation products and G) To induce the enzymes of glutathione synthesis and other antioxidant protective enzymes" (Maczurek, 2008).

Through both lowering oxidative stress and insulin resistance, lipoic acid may help disrupt the pathogenesis of AD. The pathogenesis of Alzheimer's disease has many proposed mechanisms and contributory factors. Amyloid plaques cause a chronic inflammatory process creating oxidative stress (Hardas, 2013). This free radical-mediated injury to the brain produces lipid peroxidation and elevated cytokine levels which can be found in the CSF of AD patients (Galasko, 2012). Insulin abnormalities and insulin resistance seen in AD also may contribute to the disease pathophysiology and clinical symptoms via mechanisms mentioned above and also mechanisms that remain unknown. Described in a previous study, AD patients have impaired cerebral glucose metabolism, which partially mediated by insulin resistance, causes impaired glucose uptake and comprises acetylcholine production (Hager, 2001).

Previous Studies

An observational study done in Hanover, Germany, followed 9 patients with DSM-III-R criteria for probable AD who had received an acetylcholinesterase inhibitor 3 months prior and were given a once daily dose of 600 mg of lipoic acid. Prior to the study, the patients all were having a steady decrease in cognitive performance based off the MMSE and the ADAScog before the LA. Then after LA supplementation, there was a stabilization of cognitive function, which was demonstrated through the MMSE and ADAScog, for almost a year. (Hager, 2001)

In Italy, another observational study was done using LA. The study investigated the positive effects of LA on glucose metabolism and insulin resistance and how that affected AD progression. LA was used in two groups of AD patients, one with T2DM and one without. At the end of the study, MMSE scores significantly improved in 43% of patients in T2DM group compared with 23% in non-DM group. (Fava, 2013)

Purpose

The purpose of this study is to conduct a randomized, double-masked, single centered, clinical trial to test the hypothesis that lipoic acid is an efficacious supplement to the standard of care treatment for AD with T2DM demonstrated by an improvement/worsening in the Mini Mental State Exam (MMSE) and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) and decreased levels of biomarkers, tau, p-tau and F2-isoprostanes (F2-isops), in the CSF.

B. Statistical Analysis and Study Design

A prospectively randomized placebo-controlled trial will be performed with the goal of enrolling 80 people, 40 in Group A: AD+T2DM+LA 600mg daily and 40 in Group B: AD+T2DM+placebo. Based on prior studies, for the ADAS Cog, we would take the mean of the baseline scores and expect a reduction in score by more than nine with a SD of 16 over 2 years in the treatment group (Gillette-Guyonnet, 2001; De Jesus, 2003). Using these values, 70 subjects are required to show significance using an unpaired t-test with $p<0.05$ and power >80%. (In the ADAS Cog, increasing scores indicate worsening cognitive function.) Eighty patients will be recruited in case any patients may need to leave the study. For the MMSE, we would also take the mean of the baseline scores and expect a gain of 4 points over 2 years and use a SD of 6 as

based on prior studies. A subgroup of 10 patients in each arm of the study will receive lumbar punctures (LPs) to see if there is any difference in CSF biomarkers after the LA intervention or if there is variability throughout time, which is not associated to the treatment of AD. There is expected reduction in the biomarkers after treatment of LA, but no set data point to evaluate for significance. This data will be retrospectively evaluated between the two groups.

Seventy patients with mild-moderate AD and controlled T2DM, who have already been on acetyl cholinesterase inhibitors for 4 months, will be randomized into two groups, treatment vs. placebo, and will be evaluated over 2 years using ADAS Cog, MMSE, and CSF biomarkers (only in a subgroup). This study decided to look at only T2DM patients because the previous Italian study seemed to suggest that the greatest LA supplement benefit would be seen in the diabetic population with AD. All physicians or other health care professionals administering the MMSE or ADAS Cog will be masked to who received LA vs. placebo. Subjects must remain on their current AD medications and dosages throughout the study.

Methods of evaluation
1. Alzheimer's Disease Assessment Scale-cognitive subscale
-Evaluates language, orientation, motor skills (praxis), and memory, and is the standard instrument for measuring cognitive function in clinical trials. Takes 30-45 minutes to complete.

2. Mini-Mental Status Exam
-Evaluates orientation, memory, attention, language, and motor skills. Takes 5-10 minutes to complete. It has increased variability when compared with the ADAS-Cog and is considered not specific enough to be used alone when evaluating treatment responses. (Raetz, 2007)

3. CSF biomarkers for AD
(a) tau and p-tau
-Tau protein is an integral part of neurofibrillary tangles and neuritic dystrophy in AD. It is related to the damaged neurons and axonal processes and is elevated in the CSF in AD. (Galasko, 2012)

(b) F2-isoprostanes
-F2-isopros are a measure of lipid peroxidation in the brain. It is increased in the CSF of patients with AD and also in patients who carry mutations in presenilin 1 gene (amyloid protein precursor) that is associated with familial AD. (Galasko, 2012)

Schedule
Day 0: Baseline measurements of ADAS Cog, MMSE, and lumbar punctures for CSF biomarkers
Day 1: Subjects begin taking either lipoic acid or placebo
Month 6: ADAS Cog, MMSE
Month 12: ADAS Cog, MMSE, CSF biomarkers
Month 18: ADAS Cog, MMSE
Month 24: ADAS Cog, MMSE, CSF biomarkers

C. Study Procedure
Lumbar puncture or spinal tap
-This sterile procedure entails inserting a needle into an anesthetized portion of the lower back between two lumbar vertebrae of the spine in order to remove cerebrospinal fluid (CSF). In the CSF are biomarkers, which are elevated in AD. Risks include post-lumbar puncture headache, back discomfort or pain, bleeding, infection. This procedure would be done solely for research purposes. Likely, this procedure will take 30-45 minutes and a lumbar puncture kit will be needed. Only expect mild to moderate discomfort and inconvenience to the patient. Consent would be obtained from health care proxy.

D. Study Drugs
Lipoic acid is an approved drug in Europe for the treatment of diabetic polyneuropathy. It is a naturally occurring molecule that has been found to have antioxidant, anti-inflammatory properties as well as positive effects on glucose metabolism (Fava, 2013). Possible side effects include skin rash, lowering of blood sugar levels, and exacerbating thiamine deficiency. Subjects should not take LA if they are B1 deficient or alcoholics (Univ of Maryland, 2013).

E. Medical Device.
NA

F. Study Questionnaires
NA

G. Study Subjects
Inclusion criteria:

- Probable AD diagnosis via the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association - NINCDS/ADRDA criteria
- Age 55 years or older
- MMSE between 15-26
- Stable dose of cholinesterase inhibitor and/or memantine for 4 months to beginning the study
- No use of other antioxidant supplements unless had been taking stable dose for 4 months prior
- Geriatric Depression Scale (GDS) - Score of < 5
- Sufficient language skills to complete all testing with translating if needed
- Diagnosis of diabetes currently controlled on medication, not insulin
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Exclusion Criteria:

- Non-AD dementia
- History of stroke with neurologic deficits > 6 months after diagnosis
- Uncontrolled DM or insulin dependent DM
- Lipoic Acid supplementation less than 1 month prior to beginning of study

(Lipoic acid, 2013)

H. Recruitment of Subjects
Potential subjects will be indentified through the neurology clinic or inpatient at CUMC.

I. Confidentiality of Study Data
All patient data obtained for the study will be de-identified and given a unique patient-corresponding code to safeguard the confidentiality of the study data and the study subjects. We will have one document with the names of the patients and their unique codes, which will only be available to the study coordinator and primary investigators. Data will be stored in encrypted and password protected computers.

J. Potential Conflict of Interest
No potential conflicts of interest.

K. Location of the Study
The study will be conducted at the CUMC Neurology outpatient clinic.

L. Potential Risks
Patients that undergo the lumbar punctures face the greatest amount of risks in this study. Overall, patients may not experience improved or stabilized cognitive functioning from lipoic acid supplementation. Subjects may have to drop out of the study if they need their medications changed.

M. Potential Benefits
Subjects may experience a stabilization of their cognitive decline or experience a small cognitive improvement.

N. Alternative Therapies
NA

0. Compensation to Subjects
NA

P. Costs to Subjects
NA

Q. Minors as Research Subjects
NA

R. Radiation or Radioactive Substances
NA

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