Carbidopa-levodopa in Neovascular AMD

Study design: Prospective, open label, two-parallel group

PI: Robert W. Snyder, MD, PhD, PC

Unique Protocol ID: 0001

Protocol Version 4

Date: June 24, 2017

IND Number: 132078

ClinicalTrials.gov Identifier: NCT 03022318

Study 001: Short term effects of carbidopa-levodopa in Neovascular AMD

Synopsis

In 2008, Dr. Brian McKay identified a receptor, GPR 143, on the surface of RPE cells and discovered that L-DOPA was the natural ligand or stimulator of GPR143. He showed that treatment of RPE cells with exogenous L-DOPA resulted in the release of additional PEDF. In subsequent work his group also showed that L-DOPA stimulation of PEDF in RPE cells was also associated with a decrease in VEGF. Thus, McKay hypothesized that exogenous L-DOPA may prevent the onset of AMD or progression to wet AMD.

In 2015, McKay and his associates published a paper that showed that patients, who had been treated with L-DOPA, had a delay in the onset of AMD by 8 years, compared to patients who had not been treated with L-DOPA. In addition, those who had AMD and went on to develop wet AMD, did so 5 years later than those with no history of L-DOPA treatment. L-DOPA is an intermediate in the pigmentation pathway. McKay et al suggested that the reason darkly pigmented races do not get AMD nearly as frequently as lighter pigmented races, is that they produce more pigment, and thus more L-DOPA to stimulate GPR143 on RPE cells. According to this hypothesis, the stimulated RPE cells release PEDF and decrease VEGF, which together are responsible for the protective effect.

Since there are no established animal models for AMD, and L-DOPA has a good safety profile in healthy volunteers and patients with Parkinson's disease, we initiated a prospective trial to show efficacy in patients with neovascular AMD. This trial is in patients who have not had intraocular anti-VEGF injections. This trial will also evaluate the safety and tolerability of L-DOPA, in this population of patients with Wet AMD. The patients will be made aware of potential side effects of L-DOPA.

Design: Prospective, two parallel group, open label

Objectives

1 To determine whether L-DOPA-carbidopa supplementation can improve or stabilize the anatomic findings on OCT, within 30 days, in patients with choroidal neovascular AMD.

2 To determine whether L-DOPA-carbidopa supplementation can improve or stabilize visual function within 30 days, in patients with choroidal neovascular AMD, by testing ETDRS visual acuity.

3 To evaluate the relative benefits of carbidopa-levodopa 25-100 mg, one tablet once daily hs and one tablet TID

4 To determine whether L-DOPA-carbidopa supplementation is well tolerated in our target group of patients with wet AMD in one eye.

Inclusion criteria

1 A diagnosis of AMD with choroidal neovascularization (CNV) in one eye.
2 Not previously treated with anti-VEGF injections.
3 Normal or dry AMD of any grade in the second eye.
4 Age 50-85 years.
5 Willingness to maintain AREDS vitamin supplements throughout the study, or remain off these supplements for the duration of the study, if not taking them prior to the study;

Treatments:

Patients receive either open label, carbidopa 25-100 mg, one tablet once daily hs for one month or one tablet dosed three times daily, in the morning, with supper and hs for one month (100 or 300 mg of levodopa daily). This is the equivalent of very low to low doses of carbidopa-levodopa in patients with Parkinson's disease.

Each patient will be reevaluated at weekly (5-8 day) intervals.

Duration: up to 32 days of treatment. This study will end with the first anti-VEGF injection, or after Visit 5, whichever occurs first. At the end of the study, patients will be eligible to enter Study 002.

Measurements and Activities:

1 Ophthalmic history and comprehensive eye examination; including visual acuity, with best correction, using an EDTRS chart, in both eyes prior to randomization, and ophthalmoscopic eye examination, and OCT;

2 Repeat assessment of visual acuity using an EDTRS chart, ophthalmoscopic eye examination, and OCT at weekly visits;

Criteria for anti-VEGF injections

This will be based on: weekly evaluation of ETDRS visual acuity (decrease of 5 letters from previous visit); increased macular thickness (compared to normal and previous visit as measured by OCT); new blood (hemorrhage on direct retinal examination; or subjective decrease in vision. If any of these criteria are met, or if, in the opinion of the Ophthalmologist, or the patient's Retina Specialist, the patient requires anti-VEGF therapy, the patient will have an anti-VEGF intraocular injection, by his or her Retina Specialist. If none of these criteria are met at visits 2, 3 or 4, with patient agreement, anti-VEGF injection will not be done, and the patient will be reevaluated in 1 week.