Sildenafil for Treatment of Choroidal Ischemia

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BACKGROUND

Research Aims & Abstracts

The hypothesis of our study is to determine if there is a benefit afforded by the use of systemic Sildenafil to patients with choroidal and retinal degenerations and dystrophies, such as vitelliform degeneration, dry and reticular AMD as well as patients with hereditary and acquired retinal dystrophies such as retinitis pigmentosa and central serous retinopathy. We theorize that Sildenafil will enhance choroidal perfusion and slow the progression of dry and reticular AMD, as well as vitelliform degneration, and the associated decrease in vision, as well as reduce the frequency of intraocular injections of anti-VEGF medications. In addition, in patients with acquired retinal conditions such as central serous retinopathy we theorize that sildenafil will enhance resorption of sub-retinal fluid.

We have shown that choroidal insufficiency is one of the causes of macular degeneration. Vitelliform degeneration has been shown to have deposits in the macula that are the same as those in AMD. We have, in a small, off-label series of patients, found that Sildenafil, the generic form of Viagra, can increase choroidal perfusion, and possibly delay or ameliorate AMD, and it should have a similar effect in retinal degenerations and dystropies or other choroidal degenerative conditions. The drug being offered is Sildenafil similar to the dosage used to treat other diseases such as pulmonary hypertension. The only contraindication that we are aware of is that it cannot be used on patients taking nitrates for heart disease.

Study Purpose and Rationale

Age-Related Macular Degeneration (AMD) is a sight-threatening visual disturbance that affects the macula in older ages. It is irreversible if the pigment epithelium is lost, but wet AMD can be arrested or delayed with the use of intraocular injections of 3 compounds at this time:

1. Avastin: an anti-VEGF (Vascular Endothelial Growth Factor) drug used in ophthalmic off-label use for AM, manufactured by Genentech

2. Lucentis: an Anti-VEGF drug with FDA approval also by Genentech.

3. Eyela: a VEGF trap drug developed by Regeneron.

All three drugs are injected into the eye in minute doses of usually 0.1 mL. These are usually injected at 4 to 6 week intervals and treatment may be extended for several years. Different

patterns of injection times are followed but usually are monthly for 12 or more months, or monthly for 3 months and then extended observation at monthly intervals unless vision declines or OCT shows recurrence of fluid in the retina. Vitelliform macular degeneration is a disorder that causes visual loss due to deposits of liopfuscin in the macula, which have been shown to be identical to the deposits seen in macular degeneration. The goal of therapy in our proposal is to reduce or eliminate the number of injections by slowing down transformation of dry to wet AMD in treated patients, or to slow progression of visual loss in vitelliform and age-related dry AMD as well as other macular, retinal and choroidal degenerations and dystrophies. Sight preservation is the ultimate goal, using a systemic drug that reduces the need for injections where indicated.

We wish to continue a study of the effects of PDE-5 and PDE-6 inhibitor drugs such as Sildenafil (Viagra) on the choroid, which we have shown to be ischemic in most dry age-related macular degeneration (AMD) (BJO 2013). We have also shown that Sildenafil (Viagra) can increase both choroidal thickness and perfusion in normal subjects. Sildenafil is used in medicine to increase blood flow in such diseases as pulmonary hypertension and Reynaud's disease. The only contraindication of these anti-VEGF drugs is the concomitant use of nitrates, as it could lower blood pressure.

A small off-label clinical series of patients with AMD (four patients) has indicated a beneficial result in two areas: a longer time between injections of Lucentis for AMD and increased contrast sensitivity. In addition, one patient had rapid resolution of subretinal drusen material. Thus, a reduced requirement for injections for wet AMD and heightened or brighter environmental viewing are possible. In dry AMD we are hoping for delay of conversion to the wet form and possibly reduction of drusen in dry AMD.

We plan to study the results for Sildenafil 20 - 40 mg orally two times a day (a dosage used in treating pulmonary hypertension) in treating vitelliform degeneration or dry AMD, including patients who have had wet AMD in the fellow eye. A small cohort of patients who have a form of dry AMD termed Reticular AMD will also be studied. This form of AMD has small drusen that present as "pox-like" finely scattered drusen that can progress to AMD. Patients with Reticular AMD offer the advantage of small lipid volume and thus are a potentially easier group to quantify resolution using a PDE-5 and PDE-6 inhibitor such as Sildenafil. In addition, we will include other degenerative diseases of the choroid and retina as well as hereditary and acquired retinal

dystrophies, such as central serous retinopathy and retinitis pigmentosa, that may benefit from increased choroidal blood flow.

Study Design

Patients will be enrolled to receive Sildenafil as part of the study. We will also review records of patients who are receiving Sildenafil as part of their standard of care. The study will enroll up to 25 patients with dry AMD, reticular AMD or a combination of wet and dry AMD as well as other macular, retinal and choroidal degenerations and dystrophies. The visual acuity and ocular coherent tomography (OCT) evaluation will be performed as noted under study procedures. We plan to continue the study until up to 25 patients have completed five years of follow-up. This will include patients who are receiving Sildenafil as part of the study and patients who receive Sildenafil for standard care whose charts will be reviewed.

Criteria of visual acuity and number of Lucentis (or other anti-VEGF drugs) injections will be monitored and compared with well documented studies using Lucentis or Avastin or Eylea. OCT and ultrasound measurement of drusen change will be performed and quantified by size and number of drusen.

Patients referred for diagnosis and treatment of AMD as well as other macular, retinal and choroidal degenerations and dystrophies in the practices of Columbia Ophthalmology doctors will be offered inclusion in the study if they have drusen and normal vision in at least one eye. In the course of the study, measurements of vision and Optical Coherence Tomography (OCT). Fundus photography will also be performed at initial exam and if changes are noted on OCT or clinical exam. Visual acuity will be measured.

Systemic Sildenafil will be prescribed for twice a day use. Initial Sildenafil dosage will be weight dependent. Patients will start at 40 mg daily (20 mg in the morning, 20 mg in the evening) or 60 mg daily (40 mg in the morning and 20 mg in the evening). The patient will be followed monthly or bi-monthly as is usual. Sildenafil dosage may be increased to up to 80mg daily (20-40mg in the morning and 20-40mg in the evening) based on the response to lower doses. If the subject has not had improvement after initial treatment, their dose may be increased, at the discretion of the study physician.

Visual acuity along with OCT will be performed at each visit. If available, ultrasound perfusion measurements will be performed within approximately 6 months of starting medication

and approximately 12 months after starting medication. Patients will be treated with Sildenafil only if they choose to enroll in the study.

Patients with AMD will continue to take sildenafil until otherwise directed. Patients with retinal dystrophies and degenerations will take sildenafil until otherwise directed. Patients with central serous retinopathy and other dystrophies with fluid-filled structures will stop one month after OCT testing shows a resorption of fluid from ocular structures. If the fluid-filled structures return, we may restart sildenafil treatment after observing these structures on OCT.

STATISTICAL PROCEDURES

Statistical evaluation will be provided for data using a standard T-test. Patients will be asked to participate for a period of up to 5 years. Results are deterministic, either drusen will improve or they will not. Secondly, the period between injections for wet AMD will be extended or not, compared to the standard treatment protocol. Improvement or maintenance from baseline of visual acuity, contrast sensitivity and OCT and fundus appearance are the end points.