Biomere

COMMUNITY BLOG

LEVODOPA IMPROVES VISION IN NEOVASCULARIZED AMD

Levodopa or L-dopa was approved 50 years ago as a treatment for Parkinson's disease (PD) to replace dopamine in the brain and slow disease progression. Levodopa has been prescribed to millions of PD patients as the first line of treatment. The drug is a modified amino acid (L-dihydroxyphenylalanine) that is able to cross the blood brain barrier where it is metabolized into dopamine and taken up by dopaminergic neurons.

Age-related macular degeneration or AMD presents in two forms – the more prevalent dry AMD and the less prevalent neovascularized or wet AMD (nAMD). Neovascularized AMD develops when abnormal blood vessels grow under the macula and leak blood and fluids that damage photoreceptor cells. This form of AMD represents 10-15% of all AMD patients, but 90% of the patients develop vision loss. Currently, nAMD is treated with anti-VEGF therapies like bevacizumab (Avastin®) and ranibizumab (Lucentis®) that are injected into the eyes every few weeks. While these therapies are effective, they require frequent injections and are expensive. Due to this trend, there is a large clinical need for improved and affordable therapies for nAMD. An interesting retrospective study in 2016 reported that PD patients who were prescribed L-dopa were less likely to develop age-related macular degeneration (AMD), and those who developed AMD had a later onset compared to the mean age of onset for AMD.
What if levodopa, which is a safe and well tolerated therapy, could help delay the need or frequency of anti-VEGF injections? To answer this question, two proof of concept studies were performed in Tucson, Arizona. In the first study, 20 newly diagnosed nAMD patients were dosed with Levodopa and then tested for visual improvement and acuity over 32 days. The second study was a dose range study with 35 patients. Both studies showed that levodopa induced significant improvement in vision and retinal anatomy including central retinal thickness and retinal fluid. The dose ranging study reported limited adverse events suggesting that levodopa is well tolerated and a viable option for advanced AMD patients.

How does levodopa work in the retinal pigment epithelia? A G-protein coupled receptor (GPCR) called GPR143 is expressed in retinal pigment epithelial cells and the ligand for this GPCR is levodopa. GPR143 is involved in melanin synthesis via the biogenesis, organization and transport of melanosomes in pigment epithelial cells. One of the signaling factors that is expressed in retinal epithelial cells is PEDF (pigment epithelium-derived factor), an anti-angiogenic factor that is downregulated along with melanin in aged populations. nAMD patients tend to be older so the downregulation of PEDF and upregulation of VEGF induces the formation of abnormal blood vessels in nAMD patients. Levodopa acts by flipping the angiogenesis balance – PEDF expression is upregulated and VEGF expression is downregulated.

It's important to note that levodopa is likely not a replacement for anti-VEGF therapies and more work needs to be done including expanded clinical trials that include a control arm, and segmentation of the results by racial diversity and other known factors that contribute to nAMD development. These studies show that levodopa has the potential to be a safe and effective adjunct therapy to help manage the use of anti-VEGF injections in the treatment of neovascularized AMD.

Interested in learning more about the clinical results?
Check out the **paper** published in July 2020 and the proof of concept **clinical trial 1** and **clinical trial 2**.