

Topical Tubulin Inhibition for Exudative AMD

A promising new approach.

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OcuCure Therapeutics, Inc.'s (Roanoke, VA) lead compound, OC-10X, is a selective tubulin inhibitor under development for the treatment of age-related macular degeneration (AMD). When administered as a topical eye drop, OC-10X has demonstrated both antiangiogenic (inhibition) and angiolytic (regression) properties in animal models of AMD. Unlike other therapies, OC-10X provides the efficacy of a vascular targeting agent without the traditional toxicity and works downstream independently of growth factors. As demonstrated by OcuCure's preclinical data, tubulin inhibition may be a promising new approach to the treatment of AMD.

TUBULIN INHIBITION

Tubulin is a protein dimer composed of α and β subunits that forms microtubules, which are essential to cellular functions like mitosis, transport, and cytokinesis, and also help form the cell cytoskeleton. There are tubulin inhibitors currently available, including vinca alkaloids, taxols, and colchicine, all of which are used in oncology. Combretastatin, which is also a tubulin inhibitor used in oncology, is currently being investigated for the treatment of AMD. Most tubulin inhibitors, however, have significant toxicity, giving them a narrow therapeutic window and an adverse effect on normal cells.

OC-10X

OcuCure's compound, OC-10X, is a quinazolinone, which is highly lipid soluble and has an extremely low molecular weight of 300 Daltons. OC-10X is available in a topical eye drop formulation, which, in animal studies, achieved therapeutic concentrations at the vitreous, retina, and choroid levels. The compound also demonstrated an excellent safety profile and non-toxicity. OC-10X inhibits tubulin in proliferating vascular endothelial cells and works independently of vascular endothelial growth factor (VEGF) and all other growth factors.

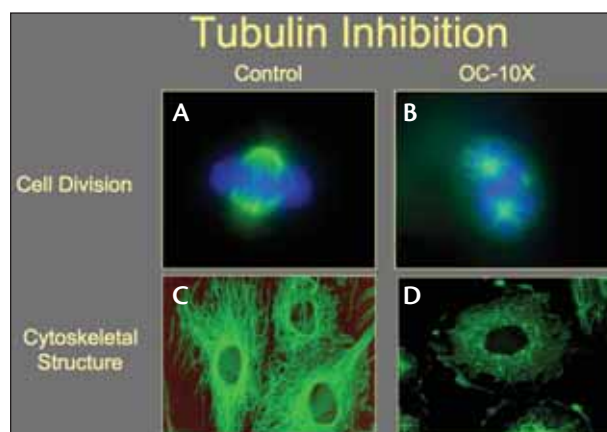


Figure 1. OC-10X's mechanism of action in cell division and the cytoskeletal structure.

Figure 1 illustrates tubulin inhibition; Panel A shows normal cell division, and Panel B shows OC-10X disrupting cell division during interphase. In Panel C, there is the normal cytoskeleton structure, and in Panel D, OC-10X depolymerized tubulin and disrupted the cytoskeletal structure. Figure 2 shows the antiangiogenic activity of OC-10X in a chicken embryo chorioallantoic membrane assay. There is normal vascularization around the control ring, and in a ring containing OC-10X, there is reduced angiogenesis.

OC-10X is a potent inhibitor of human endothelial cell proliferation in micromolar quantities. In cell culture, OC-10X achieved about 70% inhibition of retinal arterial endothelial cells, independent of VEGF (Figure 3).¹

The tubulin binding site (Figure 4) may be important in understanding the mechanism of action of OC-10X. Although other tubulin inhibitors bind at the Colchicine Binding Site, OC-10X binds at a different site and may be responsible for its limited toxicity.

ANIMAL MODELS WITH OC-10X

At the 2008 Annual Meeting of the Retina Society in

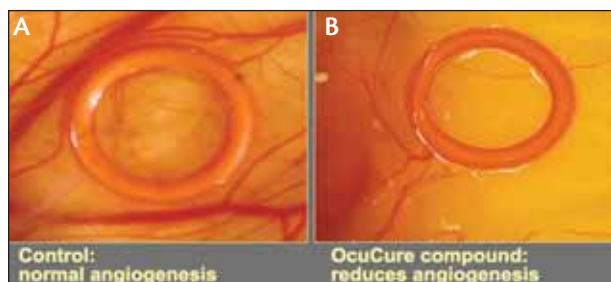


Figure 2. Antiangiogenic activity of OC-10X in an in vivo chicken chorioallantoic membrane assay.

Scottsdale, Arizona, we presented data from a study evaluating the efficacy of OC-10X in a Brown Norway rat model of AMD.² The results showed that topical OC-10X demonstrated significant antiangiogenic and angiolytic activity as well as a mean 40% reduction of choroidal neovascularization (CNV), which was statistically significant ($P < .05$).

A second study was conducted to determine OC-10X's efficacy in a nonhuman primate model of CNV. Using laser photocoagulation, CNV was induced in both eyes of eight nonhuman primates. At the time of laser and 2 weeks later, one eye of each animal received an intravitreal injection of OC-10X while the fellow eye served as the control. Despite having topical agents, intravitreal agents were used because frequent topical administration is impossible in non-sedated animals. At 4 weeks, the animals were sacrificed, and the area of CNV was measured using the fluoresceinylisothiocyanato-dextran (FITC-dextran) technique. Overall, eyes treated with OC-10X had a 43% reduction in CNV compared with control eyes.

Pharmacokinetics were studied in a second group of 10 nonhuman primates, who first received general anesthesia.³ Each animal was given three bilateral topical doses of carbon 14 radiolabeled OC-10X administered 30 minutes apart. They were euthanized 1 to 4 hours later, and the concentrations of OC-10X were then determined. With just three topical doses, there were clinically significant levels of the drug in the vitreous (177 ng/gm) and retina (22 ng/gm). Peak retina concentrations may also increase as OC-10X distributes to the posterior segment. Additionally, there were trace amounts of OC-10X in plasma and no accumulation in peripheral organs.

In a 16-month safety study conducted in a rat model, there was no evidence of ocular toxicity by intraocular pressure, confocal microscopy, electroretinogram, multifocal electroretinogram, visual evoked potentials, and histologic evaluation of the globe, including the cornea and the retina (data on file, OcuCure Therapeutics, Inc.).

SUMMARY

With topical administration in our nonhuman models,

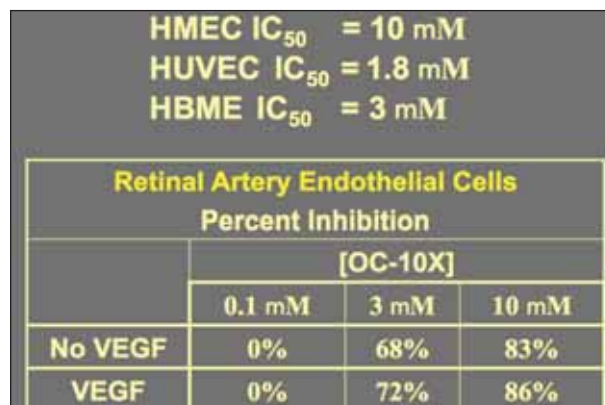


Figure 3. OC-10X inhibited retinal arterial endothelial cells, independent of VEGF.

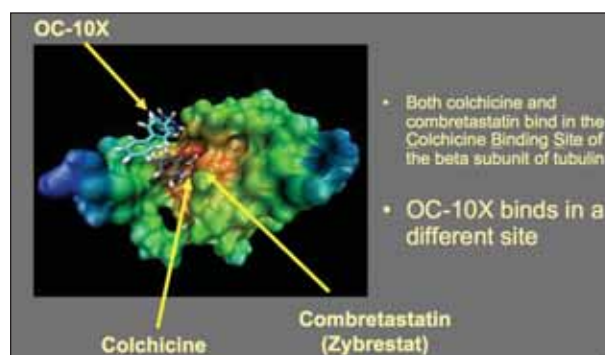


Figure 4. The tubulin binding site of OC-10X compared with that of other tubulin inhibitors.

we found no evidence of any ocular or systemic toxicity, and we achieved what we feel are therapeutic levels of OC-10X in the retina, vitreous, and choroid. Tubulin inhibition, therefore, may represent a promising new approach to the management of CNV in AMD, diabetic retinopathy, and hopefully other retinal diseases. ■

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