Evaluation of Biocompatibility of a Novel Sustained Ocular Drug Delivery System in Rhesus Macaques Using Optical Coherence Tomography Imaging

Zhe Wang[1], Monica Motta[2], Ariana Marangakis[2], Soohyun Kim[3], Glenn Yiu[4], Sara Thomasy[2,3], Jennifer Kang-Mieler[5]

[1]School of Veterinary Medicine, University of California, Davis, Davis, CA; [2]Department of Ophthalmology and vision Sciences, School of Veterinary Medicine, University of California, Davis, Davis, CA; [3]Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California Davis, Davis, CA; [4]Department of Ophthalmology and Vision Science, University of California Davis, Sacramento, CA; [5] Illinois Institute of Technology, Department of Biomedical Engineering, Chicago, IL

Introduction

1) Current intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for treatment of the wet form of age-related macular degeneration (AMD) and other retinal diseases requires frequent injections that are associated with socioeconomic cost and risk for adverse events for the patients.
2) Biodegradable microspheres suspended within thermoresponsive hydrogel designed by Dr. Kang-Mieler's team can be used as an ocular drug delivery system (DDS). This DDS can achieve controlled and extended release of anti-VEGF agents, with potential to reduce intravitreal injection frequency.
3) They have demonstrated excellent biocompatibility and pharmacokinetic properties of this DDS in a laser-induced choroidal neovascularization (CNV) rodent AMD model.
4) Nonhuman primates are the only mammals to possess a true macula similar to humans, making them ideal models for macular diseases.

Hypothesis

Similar to rodent models, this ocular DDS is safe and biocompatible with no toxicity to primate eyes.

Methods

1) The right eyes of 3 healthy *rhesus macaques* received 50 uL (0.0282 ug/uL) intravitreal injection of aflibercept-loaded DDS in January 2017 with the left eyes served as control. All animals underwent complete ophthalmic examinations including spectral domain-optical optical coherence tomography (SD-OCT) and electroretinogram (ERG) before injection.
2) Animals continued to undergo ophthalmic exam and imaging at monthly intervals after injection until 6 months after initial therapy.
3) SD-OCT images taken with the Heidelberg Spectralis device were evaluated for anatomic change in retina. Quantitative measurement of retinal layer thickness was obtained using Heidelberg Eye Explorer software.
4) ERG results obtained with the LKC Technologies UTAS Visual Electrodiagnostic System was exported for analysis of retinal cellular function.
5) Effects of d   and drug time interactio   evaluated using mixed effec   of v   ersion

Selected reference

1. Brown, D.M., et al., Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology, 2009: 116: p. 57-65.
2. Osswald, C.R., et al., In Vivo Efficacy of an Injectable Microsphere-Hydrogel Ocular Drug Delivery System. Curr Eye Res, 2017: p. 1-9.
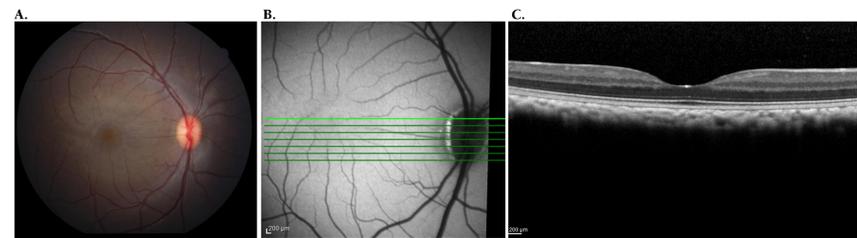
Results

Figure 1. Comparison of fundus photography (A), confocal scanning laser ophthalmoscopy (B) and spectral domain-optical coherence tomography (SD-OCT) (C) image of the retina of a *rhesus macaque* 4 months after initial hydrogel injection.
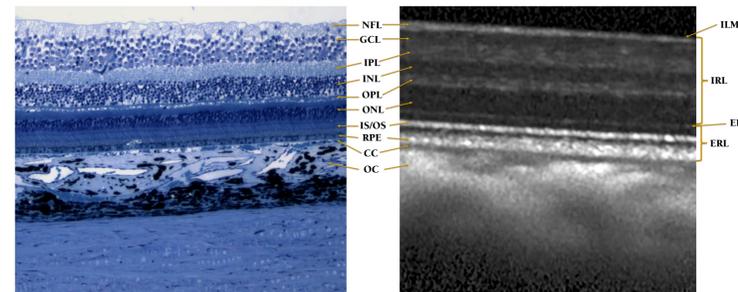

Figure 2. Comparison of high-resolution histological sections and spectral domain-optical coherence tomography (SD-OCT) images of a normal eye in an adult rhesus macaque. Abbreviations: NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; IS, photoreceptor inner segments; OS, photoreceptor outer segments; RPE, retinal pigment epithelium; CC, choriocapillaris; OC, outer choroid. ILM: internal limiting membrane; ELM, external limiting membrane; IRL, inner retinal layer; ORL, outer retinal layer.
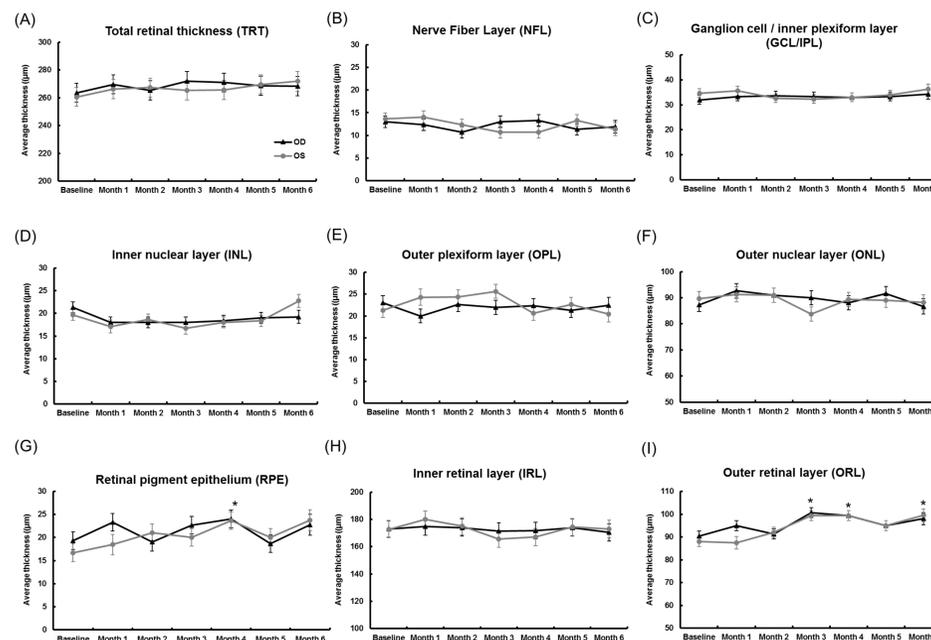

Figure 3. Comparison of retinal layer thicknesses measured of the right eye (black line) and left eye (grey line) from SD-OCT at baseline and 6 months after initial treatment. Asterisk represents there is statistically significant difference between the thickness of a certain layer at a certain time point compared with that at the baseline.

Results

Table 1. Significance of mixed effects on thickness of retinal layers

|	Time	Eye	Time*Eye
Nerve fiber layer (NFL)	0.286	0.879	0.040*
Ganglion cell / inner plexiform layer (GCL/IPL)	0.426	0.1986	0.478
Inner nuclear layer (INL)	0.019*	0.859	0.411
Outer plexiform layer (OPL)	0.366	0.245	0.081
Outer nuclear layer (ONL)	0.015*	0.354	0.067
Retinal pigment epithelium (RPE)	0.018*	0.343	0.392
Inner retinal layer (IRL)	<0.01**	0.811	0.072
Outer retinal layer (ORL)	<0.01**	0.311	0.618
Total retinal thickness (TRT)	0.034*	0.186	0.267
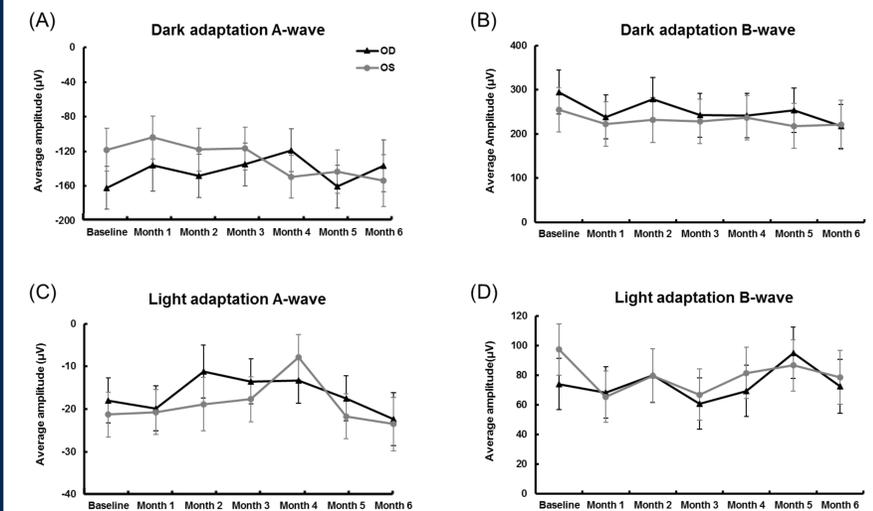
Figure 4. Comparison of ERG results from the right eye and the left eye at baseline and 6 months after initial treatment. Dark adaptation: 10 $cd \cdot s/m^2$, chromaticity (0.33,0.33) at 0.05 Hz ; background: 0.0 $cd \cdot s/m^2$; Light adaptation: 3.0 $cd \cdot s/m^2$, chromaticity (0.33,0.33) at 2 Hz, background: 30 $cd \cdot s/m^2$, chromaticity (0.33,0.33).

Table 2. Significance of mixed effects on ERG

	Time	Eye	Time*Eye
A-wave amplitude under dark adaptation	0.861	0.302	0.680
B-wave amplitude under dark adaptation	0.772	0.256	0.989
A-wave amplitude under light adaptation	0.234	0.391	0.893
B-wave amplitude under light adaptation	0.013*	0.219	0.420

Conclusions

Aflibercept-loaded novel ocular drug delivery system was safe and caused no anatomic or functional changes on the retina of 3 *rhesus macaques* after 6 months of intravitreal injection, demonstrated by absence of SD-OCT and ERG changes.

Acknowledgement