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

Zhe Wang1, Monica Motta2, Ariana Marangakis2, Soohyun Kim3, Glenn Yiu4, Sara Thomasy4,5, Jennifer Kang-Mieler5
1School of Veterinary Medicine, University of California, Davis, Davis, CA; 2Department of Ophthalmology and Vision Sciences, School of Veterinary Medicine, University of California, Davis, Davis, CA; 3Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California Davis, Davis, CA; 4Department of Ophthalmology and Vision Science, University of California Davis, Sacramento, CA; 5Illinois 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 human eye which is a crucial model 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 coherence tomography (SD-OCT) and electrotetrogram (ERG) before injection.
2) Animals continued to undergo ophthalmic exam and imaging of 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 a mixed effect antiendothelial interaction of drug was evaluated using fluorescein angiography.

Results


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

<table>
<thead>
<tr>
<th>Eye</th>
<th>Time</th>
<th>Time*Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-wave amplitude under dark adaptation</td>
<td>0.861</td>
<td>0.302</td>
</tr>
<tr>
<td>B-wave amplitude under dark adaptation</td>
<td>0.772</td>
<td>0.236</td>
</tr>
<tr>
<td>A-wave amplitude under light adaptation</td>
<td>0.224</td>
<td>0.391</td>
</tr>
<tr>
<td>B-wave amplitude under light adaptation</td>
<td>0.013*</td>
<td>0.210</td>
</tr>
</tbody>
</table>

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

This study is supported by School of Veterinary Medicine Endowment Funds.