1. INTRODUCTION

The neovascularization and excessive vascular permeability that characterize wet age-related macular degeneration (AMD) is supported by vascular endothelial growth factor (VEGF). A number of approved drugs designed to inhibit VEGF, such as Lucentis® and Eylea®, have clinically demonstrated the effectiveness of VEGF inhibition to treat the symptoms of wet AMD. Evolving animal (Saint-Geniez, 2008; Kurihara, 2012) and human (Martin, 2012) data, however, suggests the possibility that chronic VEGF suppression may negatively influence VEGF-mediated trophic support in the normal rabbit eye following continuous VEGF inhibition. In the current study, no functional or structural changes occurred in the normal rabbit eye following continuous VEGF inhibition. In patients with neovascular AMD for at least 20 months. A single, intraocular VEGF implant delivering VEGFR is anticipated to provide equivalent or improved efficacy compared to standard-of-care therapy while eliminating the burden of frequent injections in patients with neovascular AMD. In the current study, no functional or structural changes occurred in the normal rabbit eye following continuous VEGF inhibition over a 9-month period.

2. METHODS AND MATERIALS

In these sub-groups of pharmacokinetics and toxicity evaluations of NT-503-3, rabbits were implanted for a period of 9 months. For the toxicity study, serum samples were collected at predose, on day 1, weeks 2, 4, 8, 12 and 36, analyzed for free (unbound) VEGFR and toxicokinetic parameters were calculated. Both implanted and naïve animals were terminated following 1 and 9 months, and implants removed and analyzed for VEGF production (data not shown). Repeated measurements of the retina’s inner nuclear layer (INL) and outer nuclear layer (ONL) for each of four serial sections of the retina were conducted by blinded observers. INL and ONL thickness of each animal was determined by the average of all measurements. Scotopic electroretinogram (ERG) function at 0, -16 and -24dB over 9 months was determined during predose, and weeks 4, 12 and 36 of dosing. Student’s t-test comparing treated to untreated animal eyes were performed for ERG and retina measurements. Scotopic electroretinogram (ERG) function at 0, -16, and -24dB over 9 months was determined during predose, and weeks 4, 12 and 36 of dosing. Student’s t-test comparing treated to untreated animal eyes were performed for ERG and retina measurements. For drug pharmacokinetics analysis, implanted animals sampling occurred at days 3, 7, 14, and at 1, 3, 6, and 9 months. At all time points, all study animals were sampled for VEGFR concentrations in their vitreous, aqueous humor, retina, and serum, and removed implants were analyzed for VEGF production.

3. RESULTS

VEGFR Concentrations over the Course of 9 Months Implantation with NT-503-3

A. Pharmacokinetics (PK) analysis of implanted animals. Explanted NT-503-3, vitreous, aqueous humor, retina, and serum all measured peak concentrations (Cmax) of VEGFR at 2 weeks post-implant, followed by steady-state levels of the free VEGFR protein. Systemic exposure of free VEGFR was approximately 1,000 fold lower than that of the vitreous. Demonstration of steady-state VEGFR in the retina is of particular importance, being the intended site of pharmacological action for NT-503-3 implants. B. Toxicokinetics analysis of implanted animals. Similar to the ph study, serum VEGFR Cmax occurs 2 weeks followed by steady-state levels over the remainder of the 9 months.

4. CONCLUSIONS

ECD delivery of anti-VEGF therapy has demonstrated clinically meaningful improvements in visual acuity and reductions in macular thickening in patients with neovascular AMD for at least 20 months. A single, intraocular ECD implant delivering VEGFR is anticipated to provide equivalent or improved efficacy compared to standard-of-care therapy while eliminating the burden of frequent injections in patients with neovascular AMD. In the current study, no functional or structural changes occurred in the normal rabbit eye following continuous VEGF inhibition over a 9-month period.

5. REFERENCES


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