Systemically administered Aflibercept protects against the development of neovascular lesions in the mouse laser-induced choroidal neovascularization model

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Introduction

Vascular endothelial growth factor (VEGF) plays an important role in abnormal angiogenesis in several ophthalmological diseases, such as diabetic macular edema, age-related macular degeneration and others. Studies have demonstrated that intravitreally administered aflibercept significantly decreases formation of neovascularization in the choroidal neovascularization (CNV) model. However, little is known whether systemically administered aflibercept exerts its effects on pathological choroidal neovascularization in rodents.

In the current study we aimed to study the efficacy and dose-dependency of systemically administered aflibercept (Eylea®) on the development of choroidal neovascularization.

Methods

CNV induction

CNV was induced by damaging Bruch's membrane using a 532 nm diode laser in 10-week old male C57Bl/6J mice (n=5/group). Successful rupture of Bruch's membrane was verified by fluorescein angiography (FA; Spectralis HRA2, Heidelberg Engineering, Germany) and spectral-domain optical coherence tomography (SD-OCT; Envisu R2200, Bioptigen/Leica Microsystems, USA).

Treatment

Aflibercept (Eylea®, Bayer AG, Germany) was administered as an i.p. injection at a dose of 5 mg/kg, 15 mg/kg and 25 mg/kg the day before CNV induction and every third day thereafter until the end of the 14-day study period.

Data Analysis

Longitudinal *in vivo* imaging using FA and SD-OCT was performed on days 0, 5, 10 and 14. Choroidal flatmounts were prepared and labelled with Fluorescein labelled isolectin GS-IB_4.

Qualitative and quantitative analysis of the lesions were performed from the FA scans. CNV volumes were measured from SD-OCT images using the Aiforia® platform (Aiforia Technologies, Finland). A convolutional neural network (CNN) model was trained to recognize and quantify the CNV lesion using semantic segmentation and supervised learning.

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Results

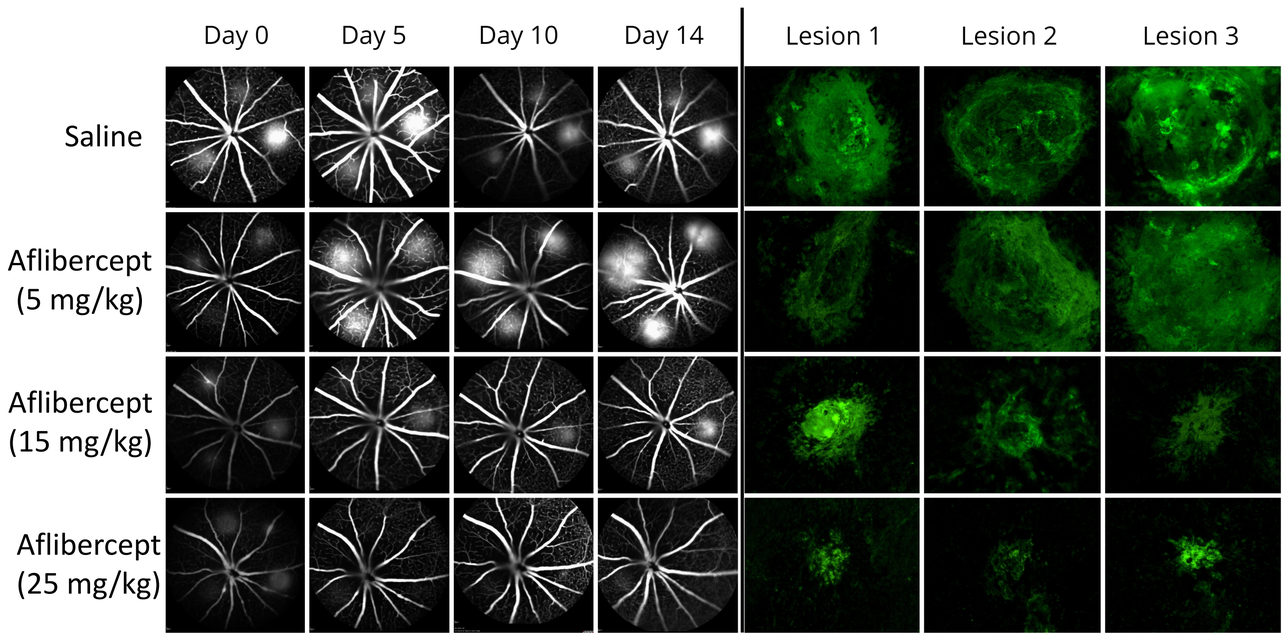

Figure 1. Retinal leakage shown as FA choroidal scans (left panel) and representative images of CNV lesions are stained using isolectin GS-IB_4 at Day 14.

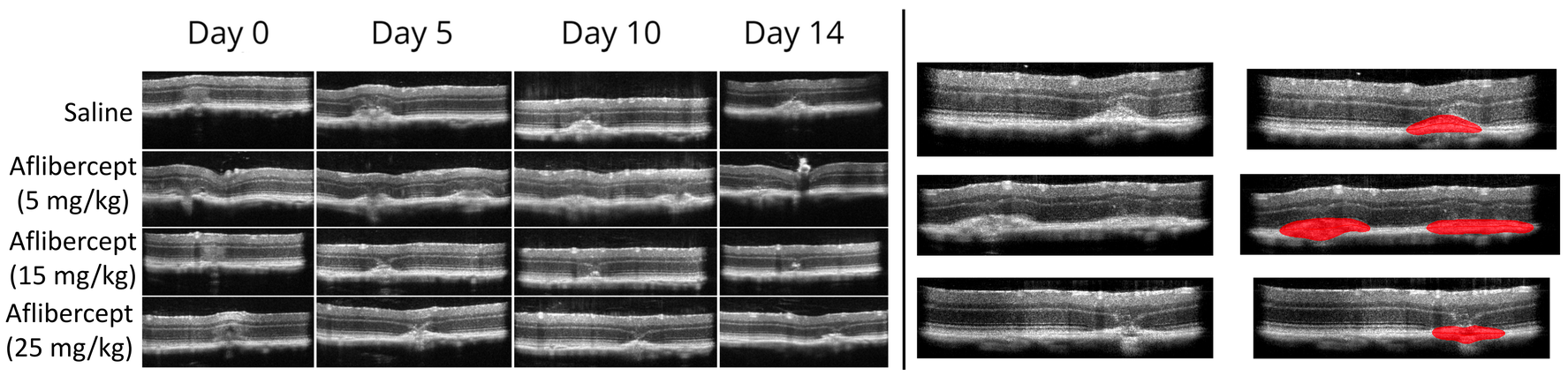

Figure 2. Sample OCT images showing lasered sites with Bruch's membrane damage on Day 0 (immediately after lasering), and subsequent CNV formation on Day 5, 10 and 14. The right panel represents example images of the automatic lesion detection and quantification using the CNN model trained with Aiforia®.

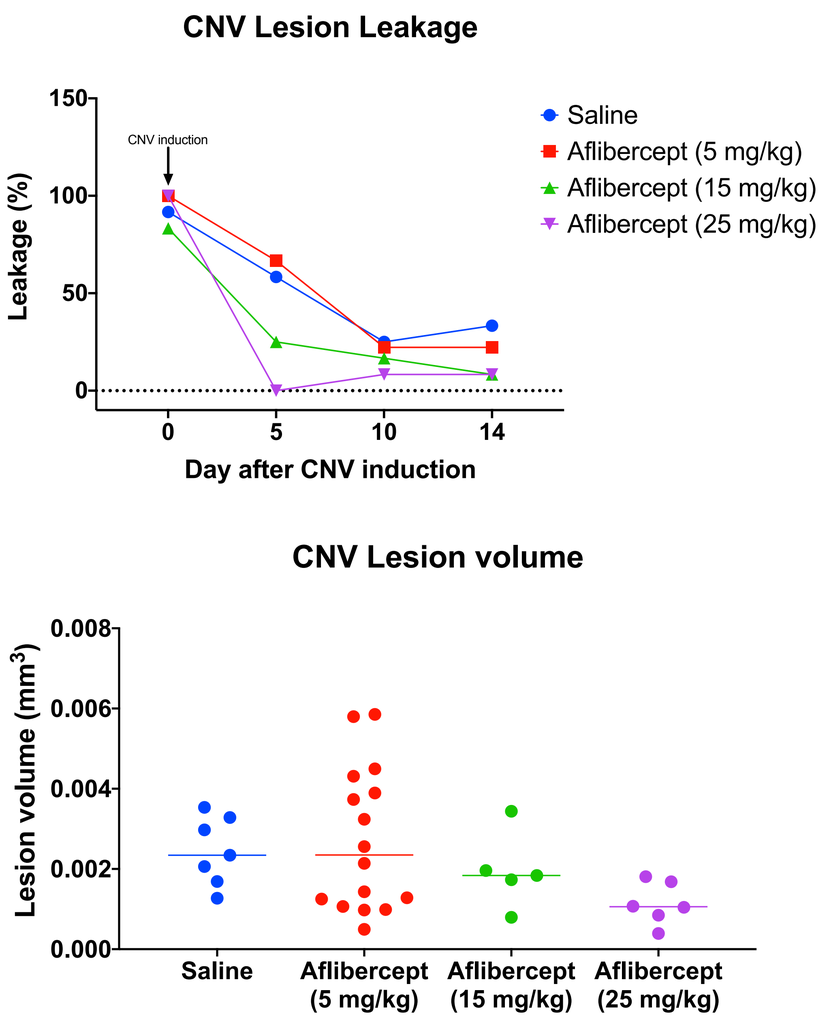

Figure 3. Intraperitoneal administration of aflibercept at the highest dose (25 mg/kg) reduced the CNV formation and vascular leak on day 5. A dose of 15 mg/kg partially decreased CNV formation and vascular leak. The lowest dose of aflibercept (5 mg/kg) did not have any effect on the CNV leakage compared to the Saline group.

The automated lesion volume analysis (CNN model) at Day 14 showed that groups treated with aflibercept at a dose of 15 mg/kg or 25 mg/kg have smaller CNV lesions.

Conclusions

Systemically-administrated aflibercept exhibited a strong dose-dependent effect on CNV formation and retinal vascular leakage. A dose of 25 mg/kg administered intraperitoneally successfully reduced the CNV formation in mice.