EXPERIMENTICA
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Deep learning-based OCT profiling and functional assessment of fingolimod treatment in experimental autoimmune encephalomyelitis (EAE)

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Purpose

We had two objectives in this study:
1. To characterize retinal neuro-degeneration and anterior visual pathway demyelination in the mouse EAE model using deep learning-assisted OCT segmentation and multimodal electrophysiology.
2. To evaluate the neuroprotective and myelin-preserving efficacy of fingolimod.

Methods

EAE was induced in C57BL/6JRj female mice using MOG_{35-55} formulated in Complete Freund's adjuvant followed by pertussis toxin. Fingolimod hydrochloride (n=14) or vehicle (n=14) were administered by oral gavage every other day from day 2. Naive mice served as controls (n=11). Disease progression was assessed by clinical scoring, *in vivo* imaging, and functional evaluation of vision.
The thickness of retinal layers and the number and area of vitreous inflammatory cells were quantified from spectral-domain OCT scans at day 42 using a pipeline based on U-Net model. Functional assessment was performed using flash electroretinography (ERG) and visual evoked potentials (VEP).
On day 42, tissues were collected. Optic nerves and cervical segments of spinal cord were stained for myelin basic protein (MBP) to assess demyelination.

Results

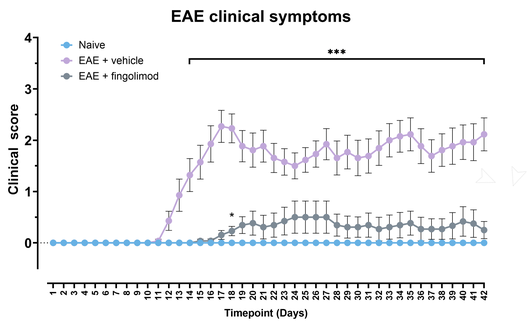

Figure 1. Development of clinical symptoms in the mouse EAE model. Fingolimod significantly reduces clinical score as compared to the vehicle-treated group (Mixed-effects model with Dunnett's multiple comparisons tests). Data are mean ± SEM (11-14 animals/group). ***P<0.001

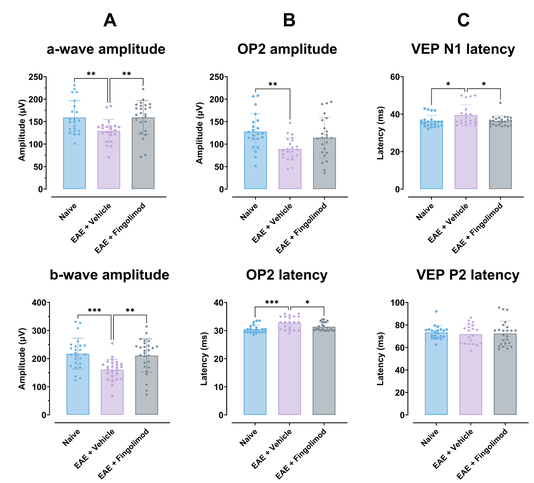

Figure 2. A-wave and b-wave amplitudes (A), oscillatory potential (OP) amplitudes and latencies (B) and visual evoked potential latencies (VEP) (C) in response to 3 cd·s/m^2 luminance flash. The data are presented as mean ± SD (11-14 animals/group, both eyes) and were analyzed using one-way ANOVA with Dunnett's multiple comparisons tests) *P<0.05, **P<0.01, ***P<0.001.

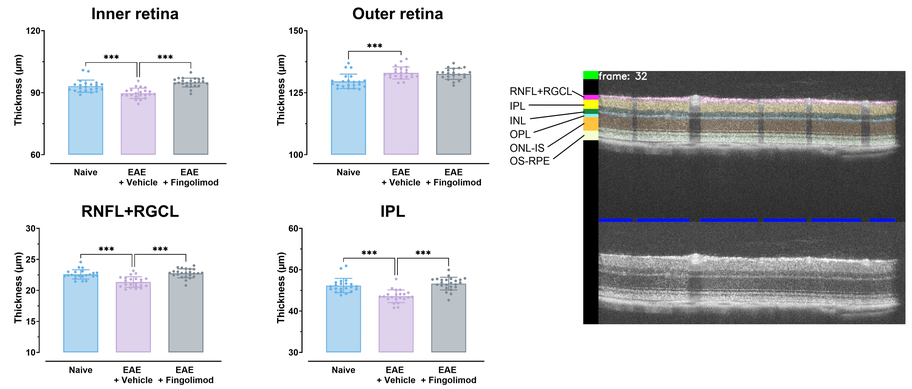

Figure 3. Retinal thickness was quantified using an algorithm detecting six different retinal layers. Fingolimod treatment preserved inner retina thickness as compared to the vehicle group. The data are mean ± SD (11-12 animals/group, both eyes) and were analyzed using Kruskal-Wallis with Dunn's multiple comparisons test. ***P<0.001. Inner retina = RNFL, RGCL and IPL.

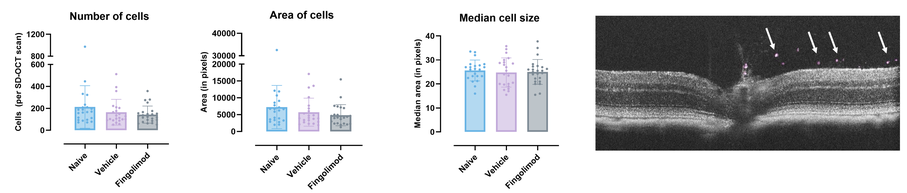

Figure 4. Quantitative analysis of inflammatory cells in the vitreous. Results show the number of inflammatory cells, total area of inflammatory cells, and median inflammatory cell size presented as mean ± SD (11-12 animals/group, both eyes. The data were analyzed with Kruskal-Wallis test.

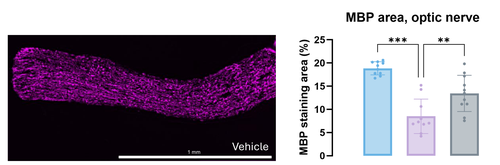

Figure 5. Myelin basic protein (MBP) area in optic nerve sections (mean ± SEM; 10-11 animals/group). The data were analyzed with Kruskal-Wallis test.

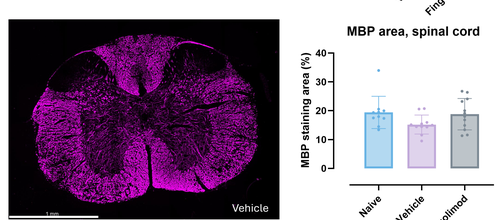

Figure 6. Myelin basic protein (MBP) area in spinal cord sections (mean ± SEM; 10-12 animals/group). The data were analyzed with Kruskal-Wallis test.

Conclusions

- Our morphological and functional data indicate that neurodegeneration in this model extends beyond RGCs, and includes dysfunction of bipolar cells, amacrine cells and photoreceptors.
- The protective effect of fingolimod across morphological and functional readouts suggests that it acts on multiple retinal layers simultaneously.
- Fingolimod provided significant protection against MBP loss in optic nerve sections, but only partial protection in spinal cord.

Disclosures
MV, AT, LT, XE, HN, NJ, SB, OV, AH, SV, AMK, PP: none
GK: Experimentica Ltd. (I,S)

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