

VEGF inhibitor reduction of microhemorrhage in immune-mediated neurologic diseases

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Introduction: Astrocyte activation and opening of cerebral endothelial cell tight junctions are distinguishing features of blood brain barrier (BBB) disruption leading to vascular leakage and microhemorrhage formation. This increase in vascular permeability has been implicated in a wide range of inflammation-induced neurological diseases. It has been observed that VEGF upregulation occurs, kinetically and regionally, with a rapid disruption of the neurovascular unit. This has led to postulations that CD8⁺ T cells induce vascular permeability by increasing VEGF expression in neurons. Using an immune-mediated murine model of BBB disruption, we quantified the changes in microhemorrhage volumes after treatment with a VEGF inhibitor.

Methods: Twelve C57BL/6 mice were intracranially infected under anesthesia with Theiler's murine encephalomyelitis virus. Seven days post infection, the mice were intravenously injected with Db:VP2121-130 peptide. The mice were divided into two treatment groups: six mice were given saline and six mice were given a small peptide VEGF inhibitor (ATWLPPR). Mice underwent T1, T2, and T2* MRI prior to and two days after treatment. Microhemorrhage volumes were calculated using Analyze 10.0.

Results: Two mice from the control group did not survive to complete the second MRI procedure and were excluded from calculations. Groups treated with VEGF inhibitor and saline showed significant increases in percentage of brain containing microhemorrhages between pre- and post-treatment MRI scans, 0.48% ($p = 0.039$) and 1.15% ($p = 0.039$) respectively. In comparing the two treatment groups, we see that the change in percentage of brain containing microhemorrhages is not statistically significant ($p = 0.168$).

Conclusion: Although no statistical significance in altering disease progression is observed when using VEGF inhibitor, the limited number of mice used in each treatment group leaves this study underpowered. Microhemorrhage volumes of the prematurely deceased mice would have likely enhanced the statistical significance of the data. This pilot study suggests a possible trend in decreasing microhemorrhage formation with VEGF inhibition treatment and demonstrates that further investigation is warranted.