Effective NAION neuroregenerative treatment using TXA127

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Purpose

Current approaches to treatment of nonarteritic anterior ischemic optic neuropathy (NAION) rely on early retinal ganglion cell (RGC) neuroprotection. However, current neuroprotective approaches have been ineffective when administered late (>1d) after induction in rodent and primate NAION models. This is particularly problematic clinically, since nearly all patients are diagnosed at least a day post-symptom onset. We report on the success of a new neuroregenerative approach using TXA127, a pharmaceutical formulation of angiotensin (1-7) currently in Phase II for ischemic stroke.

Methods

Rodent NAION (rNAION) was unilaterally induced in anesthetized Long-Evans rats (250-300g) using IV rose bengal dye followed by induction with 11 seconds of a 532nm laser light (50mW power at eye; 500um spot size). 1d post-induction, threshold animals (>500um mean optic nerve head edema) were injected with TXA127 1000ug/kg or vehicle IP and then implanted with 2ML4 Alzet pumps to deliver either TXA127 or vehicle (PBS) for 28 days. Animals were allowed to recover and visual acuity (Va) for each eye was measured by optokinetic nystagmus (Optomotry: Cerebral Mechanics, Canada) at 21-28 days post-induction X 3 sessions to identify the appropriate stable Va. Following optomotry, animals were implanted with transcranial electrodes that did not penetrate the dura, allowed to recover for one week, and then evaluated for optic nerve function using flash visual evoked potentials (fVEP) using the Celeris system (Diagnosys-Boston MA). Following euthanasia, tissue was obtained and evaluated for RGC quantification using stereology.

Results

TXA127 was well tolerated over the 28d period of time. We saw no adverse events or changes in activity/responsiveness.

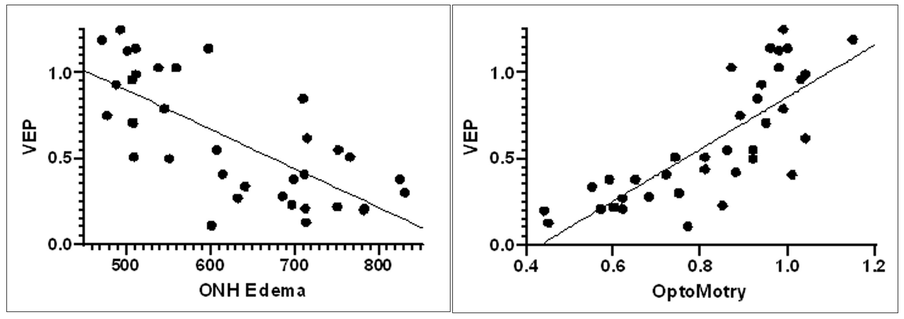
Post-induction ONH edema: The normal LE rat ONH diameter is 347±46um. We previously determined that the degree of rNAION lesion severity is closely associated with the level of post-induction rNAION edema. RGC loss is minimal in induced rat ONHs with diameter≤ 500um. Thus, the more edema, the more RGC loss and decrease in visual function, as measured by Optomotry and fVEP. rNAION-induced eyes group had mean ONH edema 643±22.9um sem (Vehicle: n=24) vs TXA treated rats 646±26.7um sem (TXA127: n=20).

Ganzfeld ERG: Animals were excluded from the study if they exhibited ERG amplitude reductions in the extracted OPs or overall pattern, compared with the uninduced side (evidence of retinal ischemia).

Visual acuity by Optomotry: Typical visual acuity is ~1.0 cycles /sec in uninduced eyes. This declines with reduced acuity. The ratio between induced and uninduced (OD/OS) eyes ranged from 0.44 (lowest) to 1.01 (highest) for Vehicle treated animals, and 0.57 (lowest) to 1.15 (highest) in TXA127 treated animals.

Visual function by fVEP: fVEP amplitudes were evaluated as a ratio of the responses of the induced/uninduced sides. This was further divided into responses from animals with mild (<600um) and moderate (>600um) ONH edema.

All summed data is shown in Figure 1. VEP vs ONH edema is shown in **Fig 1A**. VEPs declined as a function of the degree of ONH edema (regression: Pearson's r; r=-0.7169; p<0.0001, two tailed t test). VEP vs Optomotry (**Fig 1B**) revealed close correlation of the two functions, with r=-0.7877 and p<0.0001.



1A 1B

Figure 1: A. fVEP function as a measure of ONH edema. fVEP activity declines as a linear function as ONH edema increases. B. fVEP function correlates inversely with visual acuity.

TXA127 improves visual function. Measures by Optomotry and fVEP: Visual acuity was measured in vehicle and TXA127 treatment groups. This was further divided into responses from animals with mild (<600um) and moderate (>600um) ONH edema.

TXA127 treatment 1d post-induction improved visual function by both Optomotry and fVEP in animals with ONH edema >600um (**Fig. 2A and 2B**).

TXA127 treatment beginning 1 day post-induction improved RGC survival at 30d post-induction (mean RGC loss: Vehicle 74.2±4.0% vs TXA treatment 63.9±7.1%), but this difference was not statistically significant (two tailed t-test: p=0.22466; p>0.05).

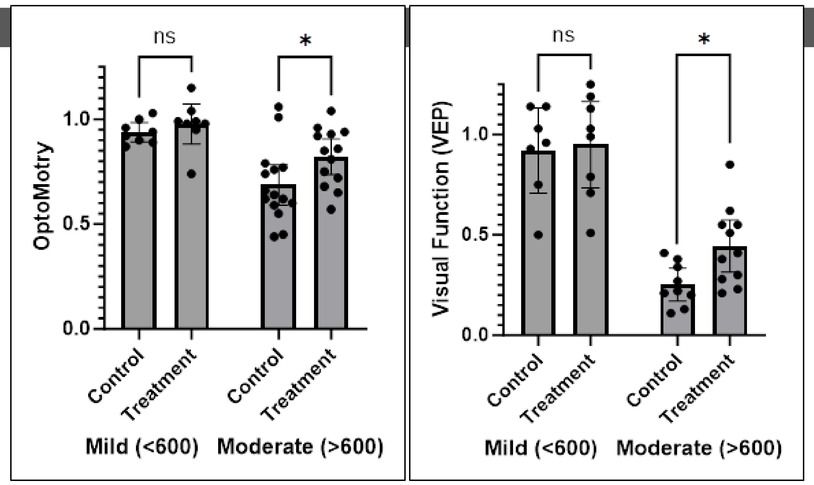


Figure 2. A. TXA127 treatment improves visual acuity 1d post-induction in animals with moderate ONH edema. B. TXA127 improves visual function by VEP in animals with moderate ONH edema. Visual function measured in vehicle and treatment groups. In both cases the ordinate is visual function, while the groups are divided into mild ONH edema (<600um ONH diameter) and moderate ONH edema (>600um ONH diameter) Treatment with TXA127 improved both visual acuity and optic nerve/visual function for both mild and moderate edema. The Neuroreparative/Neuroregenerative effects of TXA127 were significant in animals with the most edema/damage. VEP: 0.0.125 unpaired two-tailed t-test with Welch's correction. Optomotry: p=0.0325 with Welch's correction.

IBA1 immunostaining of ONH cross-sections revealed that Vehicle treated, rNAION-induced nerves had macrophage/signal intensity of 10.8±0.7% (sem), while TXA127 treated animal nerves had 8.5±1.0%. Naïve eyes had 2.2±0.2%.

Conclusions

1. TXA127 is the first neuroregenerative/neuro-reparative agent that provides protection a day after ischemic neuropathy induction.
2. TXA127's neuroregenerative effect is greatest and statistically significant in animals exhibiting the greatest degree of pre-treatment ONH edema, and RGC/axonal damage.
3. While TXA127 does provide some degree of nonsignificant neuroprotection and inflammatory inhibition in the current study, the neuroregenerative neuroreparative effects appear distinct from their protective actions.
4. This is the first drug that appears likely to have a clinically relevant time window of treatment effectiveness in NAION.

Acknowledgements

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