

Evaluation Of Micro collimated Pars Plana External Beam Radiation In The Eye.

Rishi P. Singh¹, Mark Shusterman², Darius Moshfeghi³, Tom Gardiner⁴, Michael Gertner²

¹Cole Eye Institute, Cleveland, OH ²Oraya Therapeutics, Newark, CA, ³Stanford University, Palo Alto, CA, ⁴Queen's University, Belfast, UK

Purpose:

- To evaluate a prototype stereotactic radiosurgical system delivering microcollimated external beam radiation through pars plana for choroidal neovascularization (CNV) arising from macular degeneration.

Background:

- Ionizing radiation has strong anti-angiogenic, anti-inflammatory, and anti-fibrotic effects.
- Recent data demonstrate that combining beta ionizing radiation and anti-VEGF therapy can lead to visual outcomes similar to MARINA and ANCHOR with less retreatment.
- One alternative to anti-VEGF therapy and photodynamic therapy for AMD is external beam radiation.
- Precise radiation delivery to macula can selectively inhibit proliferating endothelial cells with limited destruction of retinal tissue and no systemic side effects.

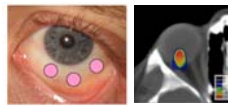
Methods:

- Five Yucatan mini-swine (10 eyes) were randomized to five treatment groups. Eight eyes were dosed with radiation on Day 1, and two eyes served as untreated controls. Treated eyes received doses up to 60 Gy to the retina and up to 130 Gy to the sclera using single or overlapping beams and delivered within 60 minutes. An x-ray device with collimated beams was used to deliver energy to the retina of each dosed eye. The treatment beams were highly collimated such that the diameter was approximately 2.5 mm on the sclera and 3 mm on the retinal surface. Fundus photography, angiography, and SDOCT were obtained on days 7,30,60, and 110. Animals were sacrificed on day 111 and gross and histopathological analysis was conducted.

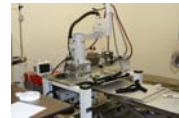
Treatment Protocol:

Group	Radiation Dosing (Left Eye)		Radiation Dosing (Right Eye)	
	Total Dose/Eye	No. of Beams	Total Dose/Eye	No. of Beams
A	60 Gray	1	Control	N/A
B	42 Gray	3	21 Gray	3
C	Control	N/A	60 Gray	3
D	21 Gray	3	42 Gray	3
E	60 Gray	3	42 Gray	1

Treatment Planning:



Location of pars plana beams with targeting of the macula.



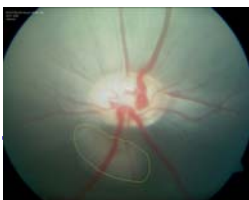
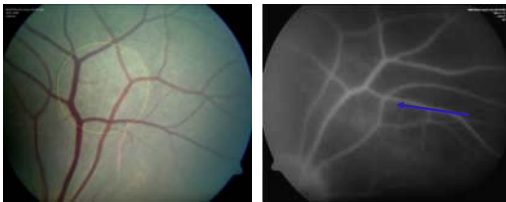
Robot delivery of micro collimated external beam radiation.

Results:

Treatment was well-tolerated and was not associated with any significant ocular anomalies up to Day 111 post-dose. Histological and gross changes to eye structures, including conjunctiva, lens, or retina were minimal.

Gross examination and histological examination of anterior segment structures revealed no abnormalities. Fundus photography, SDOCT, and fluorescein angiography were performed prior to irradiation and after at days 7, 40, 75, and 110. Each article was examined by a masked grader and evaluated for abnormalities. SDOCT of the region failed to disclose any definite abnormality in any of the treated or untreated animals. Fundus evaluation revealed no abnormalities in the clinically relevant doses of 21 Gy. There were abnormalities seen in the 42 and 60 Gy single beam eyes.

Fundus Photograph and FA Changes

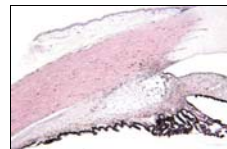


On days 76 and 111, a retinal lesion noted in the 42 and 60 Gy doses. A circular pale area of depigmentation was present. There were no retinal hemorrhages, cotton wool spots, or vascular occlusions/sheathing seen. The FA confirmed the lesion with staining seen in late frames.

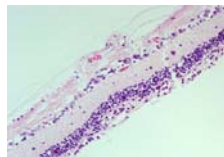
Gross and Histological Abnormalities



Gross section demonstrating change seen with 60 Gy treatment plan.



Histological examination of the anterior segment in 60 Gy treatment plan demonstrated no abnormalities despite receiving 120 Gy of direct treatment to the conjunctiva.



Center of lesions showing complete loss of photoreceptors cells

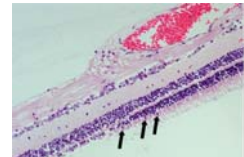


Figure shows cone nuclei displaced beyond outer limiting membrane (arrows) in penumbra of lesion.

Conclusions:

- Transcleral stereotactic radiation dosing for AMD can be accomplished using the Oraya System with no significant adverse events seen at clinically relevant levels of radiation. Further studies are being conducted with the clinical grade device to verify safety and precise targeting.