Suprachoroidal CLS-AX (axitinib injectable suspension), as a Potential Long-Acting Therapy for Neovascular Age-Related Macular Degeneration (nAMD)

Peter Kaiser, MD
Professor of Ophthalmology
Chaney Family Endowed Chair for Ophthalmology Research
Cleveland Clinic, Cole Eye Institute

Co-Authors:
Thomas Ciulla, MD, MBA
Viral Kansara, PhD

ARVO 2020 Annual Meeting
Baltimore, MD
Financial Disclosures

Current AMD Therapies Predominantly Focus on VEGF-A Blockade, not VEGF Receptors

Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers

Axitinib: Introduction

- Axitinib effectively inhibits corneal, retinal and choroidal angiogenesis in multiple preclinical models
- Axitinib has better biocompatibility with ocular cells than other tyrosine kinase inhibitors
# Tyrosine Kinase Inhibitors: Potency

## Inhibitory concentrations (IC50 in nmol) for targets with multitargeted TKIs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>VEGFR1</th>
<th>VEGFR2</th>
<th>VEGFR3</th>
<th>PDGFRα</th>
<th>PDGFRβ</th>
<th>c-Kit</th>
<th>RET</th>
<th>RAF</th>
<th>FLT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1–0.3</td>
<td>5</td>
<td>1.6</td>
<td>1.7</td>
<td>&gt;1000</td>
<td>NA</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>10</td>
<td>30</td>
<td>47</td>
<td>71</td>
<td>84</td>
<td>74</td>
<td>&gt;1000</td>
<td>NA</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>5–10</td>
<td>10</td>
<td>13</td>
<td>100–200</td>
<td>NA</td>
<td>1–10</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>NA</td>
<td>90</td>
<td>20</td>
<td>50–60</td>
<td>50–60</td>
<td>68</td>
<td>100–150</td>
<td>5–10</td>
<td>46</td>
</tr>
</tbody>
</table>
Topical Axitinib More Effectively Inhibited Experimental Murine Corneal Neovascularization than Sunitinib and Sorafenib (at same dose)

Figure 5. Selection of tyrosine kinase receptor inhibitor drugs. Screening of tyrosine kinase inhibitor drugs loaded nanowafers for their relative therapeutic efficacy in inhibiting corneal neovascularization after 10 days of treatment. Representative 3D reconstructed corneal images of fluorescence confocal microscopy: (a) healthy cornea (control); (b) untreated ocular burn (control); (c) blank PVA-NW; (d) Sora-NW; (e) Suni-NW; (f) Axi-NW. (g) Quantification of corneal neovascularization volume. n = 3 animals, *P < 0.05 vs OB control and P < 0.05 vs PVA-NW, **P < 0.01. All error bars represent standard deviation from the mean.

Axitinib inhibits angiogenic sprouts more potently than anti-VEGF-A, anti-PDGF-B and combination

Suprachoroidal Injection Procedure
Core Advantages of Treating Via the Suprachoroidal Space

**TARGETED**
The back of the eye is the location of many irreversible and debilitating visual impairments

**COMPARTMENTALIZED**
Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues

**BIOAVAILABLE**
Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug

---

Sources:
Suprachoroidal Axitinib: Ocular Distribution & Pharmacokinetics

METHOD:
- Dutch-belted pigmented rabbits
- Single bilateral suprachoroidal injection of axitinib
  - Group 1: 0.03 mg / eye
  - Group 2: 0.1 mg / eye

RESULTS

Mean concentration of suprachoroidally injected axitinib in ocular tissues for male Dutch Belted rabbits

Axitinib IC50: 0.3 nM = 0.12 ng/ mL
Suprachoroidal Axitinib: Efficacy in Brown Norway Rats

METHOD
- Laser CNV: 4 lesions per eye
- N=20 eyes (n=10 specimens, bilateral SC injections)
- Two (2) doses, days 1 & 8, 0.4 mg/eye/dose

FLUOROSCEIN ANGIOGRAPHY GRADING SCALE

RESULTS
- At Day 21: CLS-AX lesion reduction in severe (Grade IV) lesions versus control – see graph

* Fisher’s Exact p-value = .0002
Suprachoroidal Axitinib: Efficacy in Weanling Pigs

METHOD
- Laser CNV created 6 lesions per eye
- N=8 Weanling Pigs
  - OD: 4mg/ 0.1 mL Suprachoroidal CLS-AX
  - OS: 0.1 mL Saline
- Single dose followed by imaging at weeks 1 and 2

RESULTS
- SC CLS-AX significantly reduced fluorescein leakage
  - 10.5% @ week 1 (p=0.009)
  - 16.0% @ week 2 (p=0.0015)
- SC CLS-AX significantly reduced growth of new blood vessels
  - 18% reduction vs. saline treatment (p=0.03)
Suprachoroidal Axitinib: Iso-lectin B4 staining shows reduction in vascular staining in pigs

Axitinib inhibits blood vessel growth 
*(Iso-lectin B4 staining on retina flatmount)*

<table>
<thead>
<tr>
<th>Control (vehicle treated)</th>
<th>CLS-AX treated eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large area of vascular staining (red)</td>
<td>Significant reduction in vascular staining (red)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#1</th>
<th>#2</th>
</tr>
</thead>
</table>

Control (vehicle treated) | CLS-AX treated eyes |

Large area of vascular staining (red) | Significant reduction in vascular staining (red) |
AMD Vascular Endothelial Growth Factor Treatment Approaches

Current AMD Therapies Predominantly Focus on VEGF-A Blockade, not VEGF Receptors

- Anti-VEGF-A increases VEGF-C<sup>1</sup> & VEGF-D<sup>2</sup>
- Broad VEGF blockade may improve outcomes
- A Phase 2 study yielded better AMD outcomes with anti-VEGF-A,C,D vs anti-VEGF-A

Suprachoroidal Axitinib May Improve Outcomes with Its Broad VEGF Blockade

- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models<sup>3-7</sup>
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs<sup>8</sup>

Sources:
Suprachoroidal Axitinib in Animal Models

Across all animal models
- Suprachoroidal axitinib was well tolerated in all species
- No overt signs of toxicity
- Sustained, high exposure observed in ocular tissues through 10 weeks
  - Highest levels in the sclera/choroid/RPE > retina > vitreous
- No quantifiable axitinib detected in plasma or aqueous humor
Conclusion

Suprachoroidal CLS-AX has potential as a bi-annual therapy for nAMD

- Intrinsic **high potency**, pan-VEGF inhibition through receptor blockade
- **Prolonged duration** observed in PK studies
- **Pharmacodynamic effect** demonstrated in multiple animal models
- **Targeted** therapy for affected tissue layers via suprachoroidal injection