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Pharmacology Symposium

Intended vs Actual Intervals Between Intravitreal Anti-VEGF Injections and Assessment of Treatment Delays

- Christina Weng, MD, MBA, FASRS
- Nicole Somani, MD, MPH
- Daniel Olson, MD
- Jeel Mehta, BA
- Dylan McBee, BS
- Austin Huang, BSA
- Anshul Bhatnagar, BA

Objective: In patients receiving anti-VEGF intravitreal injections, are actual treatment intervals longer than intended?
Purpose: To compare the intended versus actual follow-up interval in county hospital and private clinic patients receiving anti-vascular endothelial growth factor (VEGF) injections for diabetic macular edema (DME), retinal vein occlusion (RVO), or neovascular age-related macular degeneration (AMD), and evaluate the impact of delays on visual outcomes.

Methods: Retrospective chart review of Ben Taub General Hospital and Baylor College of Medicine patients treated between 1/1/2017 and 3/1/2022 with anti-VEGF intravitreal injections for AMD, DME, or RVO. Statistical analysis was performed using Python and Excel. For each injection, the "delta" was defined as the time between actual and intended follow-up interval. Analyses were performed on a per-injection and per-patient basis with $p<0.05$ representing statistical significance.

Results: 1,881 injections (172 patients) were included in the analysis. Amongst county hospital patients (n=106), mean age was 61.1 years and most were Hispanic (63.5%). Amongst private clinic patients (n=66), mean age was 75.8 years and most were Caucasian (64.6%). Overall, the mean delta per injection was 8.4 days; the mean delta per patient was 8.3 days. A significant proportion of injections had a clinically significant delta >7 days (24.5%, 95% CI, 0.226-0.264); more of these were observed in the county versus private cohort (30.5% <county> vs. 18.1% <private>, $p<0.0001$). Amongst injections with a delta >7 days, the mean delta was 33.62 days. No clinically significant delta >7 days was observed for AMD patients; there was a clinically significant delta >7 days in DME and RVO patients, but no difference based on practice setting (DME: 9.92 days <county> vs. 12.50 days <private>; $p = 0.283$, RVO: 21.42 days <county> vs. 9.04 days <private>; $p = 0.509$). Visual acuity improved by an average of -0.0338 logMAR for eyes with delays >7 days versus -0.0027 logMAR for eyes with delays ≤7 days ($p=0.554$).

Conclusion: Nearly one-quarter of anti-VEGF injections were received at least one week later than intended; amongst injections delayed by >7 days, the average delay exceeded one month. The proportion of delayed injections and the extent of delay were greater in the county hospital versus private clinic setting. Greater delays were observed in patients with DME and RVO versus those with AMD. Eyes with longer delays trended towards lower visual gains. Efforts to improve schedule adherence are warranted to optimize visual acuity outcomes for patients.

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Pooled Safety Analysis of Aflibercept 8 mg in the CANDELA, PHOTON, and PULSAR Trials

- Philip Ferrone, MD, FASRS

Objective: To compare the safety of aflibercept 8 mg and 2 mg in the CANDELA, PHOTON, and PULSAR trials.
Purpose: To determine whether the safety profile of aflibercept 8 mg is similar to that of aflibercept 2 mg across trials.
Methods: CANDELA was a single-masked, open-label, 44-week, phase 2 trial in which treatment-naïve patients with neovascular age-related macular degeneration (nAMD) were randomized 1:1 to receive 3 monthly doses of aflibercept 8 mg or 2 mg followed by doses at Weeks 20 and 32. PHOTON is an ongoing, double-masked, 96-week, non-inferiority, phase 2/3 trial that randomized patients with diabetic macular edema 1:2:1 to receive aflibercept 2 mg every 8 weeks after 5 monthly doses (2q8) or aflibercept 8 mg every 12 or 16 weeks after 3 monthly doses (8q12 or 8q16). In the ongoing, double-masked, 96-week, non-inferiority, phase 3 PULSAR trial, patients with nAMD were randomized 1:1:1 to receive aflibercept 2q8, 8q12, or 8q16 after 3 monthly doses. Safety data were integrated across all 3 trials through Week 44 (CANDELA) and 48 (PHOTON and PULSAR).
Results: Overall, 1773 patients (aflibercept 8 mg: n=1217; aflibercept 2 mg: n=556) were treated and evaluated. Ocular treatment-emergent adverse events (TEAEs) in the study eye were reported in 35.2% and 35.3% of patients who received aflibercept 8 mg and 2 mg, respectively. The most common ocular TEAEs were reduced visual acuity (2.9% and 4.5%), vitreous floaters (3.0% and 2.7%), cataract (3.0% and 2.2%), conjunctival hemorrhage (3.0% and 2.3%), and retinal hemorrhage (2.3% and 3.1%) with aflibercept 8 mg and 2 mg, respectively. Ocular hypertension was reported in 0.8% and 0.4% of patients with aflibercept 8 mg and 2 mg, respectively, and increased intraocular pressure (IOP) was reported in 2.3% of patients in each group. Intraocular inflammation was experienced in 0.8% and 0.5% of aflibercept 8 mg- and 2 mg-treated patients, respectively. Serious ocular TEAEs were reported in 1.3% of aflibercept 8 mg-treated patients and 0.7% of aflibercept 2 mg-treated patients. Serious ocular TEAEs occurring in >1 patient in any treatment group were retinal detachment (0.4% and 0%), increased IOP (0.2% and 0%), and vitreous hemorrhage (0.2% and 0%) in the aflibercept 8 mg and 2 mg groups, respectively. There were no cases of endophthalmitis or occlusive retinal vasculitis. Adjudicated APTC events were reported in 1.5% and 2.0% of patients with aflibercept 8 mg and 2 mg, respectively.
Conclusion: Aflibercept 8 mg demonstrated comparable safety to aflibercept 2 mg across the CANDELA, PHOTON, and PULSAR trials.

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Pharmacology Symposium

12-Month Ocular Pharmacokinetic Study of EYP-1901, a Sustained-Release, Intravitreal Formulation of the Tyrosine Kinase Inhibitor Vorolanib

- Rishi Singh, MD
- Kevin Peters, MD
- Michelle Howard-Sparks, PhD
- Said Saim, PhD

Objective: EYP-1901 was evaluated for drug release and ocular and plasma pharmacokinetics following bilateral, intravitreal injection in rabbit eyes.
Purpose: Neovascularization driven by vascular endothelial growth factor (VEGF) is a major contributor to vision impairment in multiple retinal diseases. Current agents targeting VEGF are effective but limited in their ability to fully inhibit key VEGF pathways. There is also a high burden of treatment associated with traditional anti-VEGF therapies. Novel therapies targeting the VEGF pathway are under investigation to reduce burden of care and improve long-term outcomes. This study investigated the pharmacokinetics (PK) of EYP-1901, a sustained-release, intravitreal formulation of the tyrosine kinase inhibitor vorolanib in the Durasert® platform, in rabbit eyes.
Methods: Dutch Belted rabbits were administered EYP-1901 inserts in each eye by intravitreal injection. Group 1 eyes received 1 insert containing vorolanib 643 µg, and Group 2 eyes received 2 inserts containing 900 µg total. Blood samples were collected at 2,7,14, and 28 days and then once monthly for months 2-12. Inserts were recovered at 2, 7, and 14 days and then at 1, 2, 4, 6, 8, 10, and 12 months. Residual vorolanib levels were determined in all explants using high-performance liquid chromatography. The vorolanib release rate was estimated based on residual levels in the explants. Plasma and ocular tissues were separated and analyzed for vorolanib and its metabolite X-297 using liquid chromatography–mass spectrometry.
Results: The inserts released vorolanib through 12 months at an average rate of 8.1%/month in Group 1 and 7.8%/month in Group 2. The release profile displayed near zero-order kinetics through 8 months, demonstrating consistent release of microgram levels of drug each day, with concentrations in target ocular tissues (choroid and retina) above the IC50 for VEGFR2. Beyond 8 months the release rate dropped rapidly, yielding target ocular tissue levels below IC50 (<10 ng/ml) by 10 months. Vorolanib exposure rank order was choroid = retina = vitreous > aqueous humor > plasma. There was an 85%-99% drop in mean vorolanib concentration in ocular tissues and plasma between months 8 and 10.
Conclusion: EYP-1901 demonstrated sustained and consistent zero-order release of vorolanib in rabbit eyes through 8 months followed by a rapid decrease through 10 months. EYP-1901 is being studied in phase 2 clinical trials in wAMD and diabetic retinopathy, and a trial in diabetic macular edema is planned.

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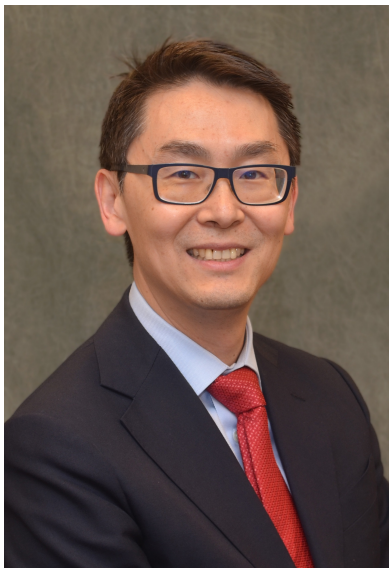
Pharmacology Symposium

ApoE-Induced Tauopathy of the Retina As a Model of Neurodegeneration



- Leo Kim, MD, PhD
- Jospeh Arboleda-Velasquez, MD, PhD
- Claudia Marino, PhD

Objective: Can a model of ApoE-induced tauopathy of the retina reproduce neurodegeneration as found in Alzheimer's disease to help develop new therapies for Alzheimer's disease?
Purpose: Alzheimer's disease (AD) is characterized by the formation of Tau fibrils leading to neurodegeneration. ApoE4 has been identified as the highest genetic risk factor for sporadic AD via its interaction with heparan sulfate proteoglycans (HSPGs) resulting in accumulation of Tau fibrils. In contrast, the ApoE3Ch Christchurch variant has been found to be a protective variant in patients with familial AD. We developed a retinal model of ApoE-induced tauopathy in order to reproduce neurodegeneration. We then show a new therapeutic approach using a monoclonal antibody targeting ApoE binding to HSPGs.

Methods: B6;C3-Tg (Jackson Laboratory, cat. 008169) male mice were injected with 2 µL of either vehicle, ApoE3, ApoE4, ApoE3Ch, ApoE4 or ApoE4 (all prepared at 50 µg/mL concentration) with 7C11.mAb monoclonal antibody designed to disrupt the ApoE binding of HSPG (950 µg/mL). Three days post injection, animals were euthanized in a CO_2 chamber. Retinas were dissected and stained for paired helical filament (PHF) Tau fibrils with anti-PHF Tau clone AT8 (1:500, ThermoFisher, cat. MN1020 and conjugated with Alexa-594 conjugation kit, Abcam, cat. AB269822). Retinas were washed with PBS and then incubated with DAPI (1:1,000 in PBS, Millipore, cat. 10236276001), and mounted using Vectashield fluoromount (Vector Laboratories, cat. H-1000-10) prior to immunofluorescence imaging.
Results: Immunofluorescence staining of dissected retina treated with vehicle, ApoE3 1.47mM or ApoE3 1.47 mM + 7C11.mAb 6 mM showed reduced accumulation of hyperphosphorylated Tau in the presence of the 7C11.mAb antibody. Quantification of the relative PHF Tau levels in ApoE3 and ApoE3 + 7C11.mAb treated retinas showed a significant reduction of PHF Tau fibrils in the presence of 7C11.mAb as compared to ApoE3 alone (p=0.0042) Immunofluorescence of retina treated with vehicle, ApoE3, ApoE3Ch, showing reduced accumulation of hyperphosphorylated Tau in the presence of the mutated Christchurch variant ApoE3Ch. Quantification of the relative PHF Tau levels in vehicle, ApoE3 (1.47 mM) and ApoE3Ch (1.47 mM) treated retinas showing significantly increased levels of PHF Tau in the presence of ApoE3 treatment as compared to ApoE3Ch and vehicle (**p=0.0055 vehicle vs. ApoE3; **p=0.0095 ApoE3 vs. ApoE3Ch; not significant Vehicle vs. ApoE3Ch). Retina intravitreally injected with 1.47 mM ApoE4 or ApoE4Ch, showed a dramatic reduction of retinal damage, and inflammation as shown by decreased levels of isolectin staining and PHF Tau accumulation with introduction of ApoE4Ch.
Conclusion: A novel model of ApoE-induced tauopathy of the retina was developed in order to assess the efficacy of 7C11.mAb disrupting ApoE-HSPG binding as a therapy for ApoE-induced tauopathy, as well as the protective effect of the ApoE Christchurch mutation. Both the 7C11.mAb and the Christchurch mutation demonstrated decreased tauopathy in this new model of neurodegeneration demonstrating a novel therapeutic approach for neurodegenerative diseases.

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Pharmacology Symposium

Population Pharmacokinetics and Safety of OPT-302, an Anti-VEGF-C/-D "Trap", in Patients With Retinal Vascular Diseases

- Dante Pieramici, MD
- Joel Naor, MD
- Ian Leitch, PhD

Objective: To describe the population PK of OPT-302, a novel anti-VEGF-C/ -D ‘trap’, to inform dosing for phase III trials and interpretation of safety and efficacy in patients with retinal vascular diseases.

Purpose: Many patients with wet age-related macular degeneration (AMD) or diabetic macular edema (DME) do not fully respond to anti-VEGF-A therapy, likely due to other mediators such as VEGF-C and D which can also drive angiogenesis and vascular leakage. OPT-302 is a novel biologic “trap” of VEGF-C/ -D, and when used in combination with VEGF-A inhibitors, improved vision and anatomic outcomes have been observed in patients with wet AMD and DME. Analysis of OPT-302 pharmacokinetics (PK) is important for interpreting safety and efficacy results and informing dosing for phase III trials. Thus, a population PK model and pooled data analysis from clinical studies in patients with wet AMD and DME were used to describe PK parameters and safety following intravitreal (IVT) OPT-302 administration
Methods: Three completed trials: two studies in wet AMD of OPT-302 ± ranibizumab (NCT02543229 and NCT03345082); and one study in DME of combination with aflibercept (NCT03397264), were conducted in a total of 569 patients (n=399 OPT-302; n=170 sham control). OPT-302 was administered via IVT injection q4w in the study eye at doses of 0.3 mg (n=8), 0.5 mg (n=120), 1 mg (n=8) or 2 mg (n=263) for up to 3 to 6 months. Safety assessments included systemic and ophthalmic evaluations, and all patients had serial serum OPT-302 concentrations analysed for PK evaluation.
Results: A total of 1,853 IVT injections were administered and OPT-302 was well tolerated across the entire dose range, with AEs being generally mild, unrelated to study drug, and/or not significantly different than anti-VEGF-A monotherapy. The population PK model following IVT OPT-302 administration was a one compartment model, with first order absorption and elimination. The concentration-time profile of OPT-302 in serum indicated low exposure of OPT-302 into the systemic circulation (C_{max} of ~20 ng/mL) with a T_{max} of ~24 hours and a linear elimination. There was no evidence to indicate that the PK of OPT-302 was altered by disease (wet AMD vs DME), age, renal function, or anti-VEGF-A co-therapy.
Conclusion: Pooled safety and population PK results provide support for OPT-302 dosing at 2 mg q4w or 2 mg q8w following 3 x q4w loading doses, selected for the wet AMD phase III studies in combination with either ranibizumab (NCT04757610) or aflibercept (NCT04757636).

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