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Wet AMD 3 Symposium

Evaluation of 8 mg Intravitreal Aflibercept Injection for Neovascular Age-Related Macular Degeneration: Results from the Phase 2 CANDELA Study

- W. Clark, MD, FASRS

Objective:
To assess the safety and efficacy of 8 mg intravitreal aflibercept injection (IAI) in patients with neovascular age-related macular degeneration (nAMD).

Purpose:
Preclinical data suggest that an IAI 8 mg may intensify and prolong the therapeutic effect of IAI 2 mg. CANDELA, a phase 2, randomized, single-masked, open-label, 44-week clinical trial (NCT04126317) assessed the safety and efficacy of IAI 8 mg versus IAI 2 mg in patients with neovascular age-related macular degeneration (nAMD).

Methods:
Treatment-naïve patients (≥50 years old) with active subfoveal choroidal neovascularization secondary to nAMD and a best corrected visual acuity (BCVA) of 78 to 24 letters (approximately 20/32 to 20/320) in the study eye were enrolled. A total of 106 patients were randomized 1:1 to receive 3 monthly doses of either IAI 2 mg (n=53) or IAI 8 mg (n=53) followed by doses at Week 20 and 32. The primary end points were safety and the proportion of eyes without retinal fluid in the center subfield at Week 16.

Results:
Overall, majority of the patients were female (62.3%); the mean (SD) age was 77.4 (8.0) years and mean (SD) baseline BCVA was 58.0 (12.1) letters. The incidence of ocular-related adverse events (AEs) through Week 16 was 17.0% (9/53) for the IAI 8 mg group and 22.6% (12/53) for the IAI 2 mg group. No new safety signals were identified; no AEs of intraocular inflammation, occlusive vasculitis, or anti-platelet trialists' collaboration (APTC)-defined arterial thromboembolic events were reported through Week 16. The proportion of eyes with no retinal fluid in the center subfield at Week 16 was 50.9% (27/53) for the IAI 8 mg group and 34.0% (18/53) for IAI 2 mg group (treatment difference, 17.0% [95% CI, −1.6%, 35.5%]; *P*=0.0770). Compared to the IAI 2 mg group, eyes in the IAI 8 mg group showed a numerically greater reduction from baseline in median central subfield thickness (−161 µm vs −96 µm), and a numerically higher increase from baseline in mean BCVA (8.4 vs 6.5 letters) at Week 16. The 44-week results will be presented.

Conclusion:
The overall safety of IAI 8 mg was similar to that of IAI 2 mg at Week 16. The observed anatomic and functional improvements with IAI 8 mg suggest potential additional therapeutic benefit over IAI 2 mg in patients with nAMD. The data support further development of IAI 8 mg.

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Wet AMD 3 Symposium

Baseline Factors Associated With 1-Year Outcomes in Phase III Comparison of SB11 (Approved Ranibizumab Biosimilar) With Reference Ranibizumab in nAMD

- Neil Bressler, MD
- Se Joon Woo, MD
- Jin Ah Jung, MD, PhD
- Taehyung Kim
- Inkyung Oh
- Mercy Yeeun Kim

Objective:
To describe baseline factors associated with one-year efficacy outcomes of a phase III randomized clinical trial comparing SB11, an approved ranibizumab biosimilar, with its reference product in neovascular age-related macular degeneration.

Purpose:
To provide ad hoc analyses regarding the equivalency of SB11 biosimilar product to its reference product, ranibizumab (rRBZ), by evaluating association of baseline factors with visual acuity and anatomic outcomes at week 52, as well as subgroup analyses judged relevant in eyes with neovascular age-related macular degeneration (nAMD).

Methods:
In a post hoc analysis of a randomized, double-masked, parallel-group, multicenter, 52-week phase III clinical trial conducted in 75 centers across 9 countries, 705 patients with nAMD were randomized to receive monthly 0.05 mL intravitreal injections of either 0.5 mg SB11 or 0.5 mg rRBZ. The primary endpoint was change from baseline in BCVA at week 8 and change in CST at week 4 with both endpoints then followed through week 52. Associations between baseline factors and treatment responses of BCVA and CST at week 52 were assessed by linear regression analyses, then multivariable analysis on baseline factors that were identified to have a pre-specified P value of <.001. Additionally, a subgroup analysis based on associated baseline factors was conducted on week 52 change from baseline for BCVA outcomes.

Results:
Among 634 (89.9%) participants who completed the 52-week visit (SB11: n=307; RBZ: n=327), the median (min, max) age was 75 (51, 96) years. For each 10-year increment of participant age, the model estimated from baseline at 52 weeks less change in BCVA letter score of 1.9 (-0.19; 95% CI, -0.29, -0.09; P<.001) letters, and greater CST reduction of 12.6 µm (-1.26; 95% CI, -1.87, -0.66; P<.001). For every 5 letter higher baseline BCVA letter score, the model predicted 1.1 (-0.22; 95% CI: -0.31,-0.14; P<.001) less letters of BCVA improvement. For every 50 µm greater baseline CST, the model estimated 35.5 µm (-0.71; 95% CI: -0.76, -0.67; P<.001) greater CST reduction at week 52.

Conclusion:
Baseline age, BCVA, and CST were predictive of visual acuity and anatomical outcomes when managing nAMD with SB11 or rRBZ. These similarities further support equivalent clinical efficacy between the products, which could reinforce confidence in the biosimilarity of SB11 with its reference product.

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Wet AMD 3 Symposium
Anti-VEGF Injection Prior Authorization Impacts on Retina Practices

- Sabin Dang, MD
- D. Wilkin Parke, MD
- Guneet Sodhi, MD
- David Eichenbaum, MD, FASRS
- Jared Nielsen, MD, MBA
- Carl Danzig, MD
- Geeta Lalwani, MD
- Nader Moinfar, MD, MPH, FACS, FASRS
- Nikolas London, MD, FACS, FASRS
- Alan Kimura, MD, MPH
- J. Michael Jumper, MD, FASRS
- Ron Lord, MD
- Veeral Sheth, MD, MBA, FASRS, FACS
- Dante Pieramici, MD
- Anton Orlin, MD
- John Thompson, MD
- Charles Wykoff, MD, PhD, FASRS

Objective:
What is the impact of the prior authorization (PA) process for anti-VEGF medications on patients and retina practices?

Purpose:
Anti-VEGF administration is the most common procedure performed by retina specialists. Increasingly, the process of obtaining authorization for these vision saving treatments is becoming more difficult. With this study we aim to quantify the impacts and results of the PA process for these medications.

Methods:
A prospective, multi-center study was performed to collect data on PA requests for anti-VEGF medications. Sites were instructed to log the results of anti-VEGF PA requests on a standardized data form. Each site logged patients where a PA request was made on a specific date of service. Any PA request submitted in anticipation for a future treatment were excluded. The data form captured which drug, the indication, the results of the PA including number of days required to get PA, and log the number of minutes required to obtain the PA. The data was analyzed using Tableau to provide descriptive statistics.

Results:
A total of 216 PA requests were recorded from 9 sites. Three PA requests were excluded as they were performed before the date of service, resulting in 213 PA requests which were included in the analysis. Overall, 204 PA requests were approved (95.7%) and 9 were denied (4.2%). Established patients requiring repeat PA for a medication they previously received was the most common indication (141 requests, 66%). Of the 204 approvals, 126 (61%) resulted in a delay in care of greater than 24 hours to receive approval for treatment, 78 PA (38%) approvals were given on the date of service. PA requests were denied for step therapy (4 requests) and uncovered diagnoses (5 requests). Bevacizumab had a 100% approval rate, aflibercept a 94% approval rate, and ranibizumab a 98% approval rate. The average employee time required to submit and obtain PA was 35.8 min, with a range of 1-240 minutes.

Conclusion:

The current data demonstrates that retina specialists are accurate and selective in their PA requests, with very few denials. Specifically, there are no instances where a request for bevacizumab was denied, suggesting the PA process for this medication is unnecessary and adds costs to retina practices as well as insurance carriers. For high-cost anti-VEGF medications, the PA approval rates were also very high (> 94%), but frequently required patients to return on a separate day to receive their treatments. The PA process has increased the burden of administering anti-VEGF treatments on patients, physicians, and insurance carriers without evidence that it prevents unnecessary treatments.

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Prior Authorization Results by Medication

Prior Authorization Results	Medication: Avastin	Medication: Eylea	Medication: Lucentis
PA was denied due to step therapy		2.17%	1.49%
PA was denied due to uncovered diagnosis		3.62%	
Same day prior authorization was obtained	50.00%	39.13%	29.85%
Unable to obtain same day authorization, but was approved later	50.00%	55.07%	68.66%

Prior authorization outcomes based on medication

Reason for PA

Patient Type / Reason for PA	
Established patient, PA required for change in medication	20.66%
Established patient, repeat PA required for a previously used medication	66.20%
Established patient, treatment naive, PA required for initiation of a new medication	6.10%
New patient requiring initiation of intravitreal injection treatment	7.04%

Reason for prior authorization request

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Novel Vascular Endothelial Growth-Factor A (VEGF-A) and Angiopoietin-2 (Ang-2) Bispecific Protein, RO-634, in Comparison to Aflibercept

- Mark Barakat, MD
- Jeffrey Olson, MD
- Jeffrey Heier, MD
- Arshad Khanani, MD, MA, FASRS
- Peter Kaiser, MD FASRS
- Ramanath Bhandari, MD

Objective:
To present pre-clinical efficacy findings of a novel bispecific protein, RO-634

Purpose:
To investigate the therapeutic effects of a novel vascular endothelial growth-factor A (VEGF-A) and angiopoietin-2 (Ang-2) bispecific protein, RO-634, for potential use in back-of-the-eye disease. In direct comparison to aflibercept, this study assesses inhibitory effects of RO-634 on human umbilical vein endothelial cell (HUVECs) migration and its therapeutic efficacy for the treatment of laser-induced CNV.

Methods:
To test inhibitory properties of RO-634 on HUVEC cell migration, HUVEC cells were grown, incubated for optimal proliferation. Culture-inserts were used to evaluate HUVEC migration potential. Thirty-five thousand HUVEC cells were seeded into a bifurcated chamber and incubated overnight. Eighteen hours after initial seeding, the culture inserts were removed and cells were washed 3x with 1x PBS. After washing, media containing 40 ng of VEGF-A was added along with either bevacizumab, aflibercept, or RO-634. Cells were incubated with the desired medium for 12 hours. The percent change in wound closure was calculated using an image of the same area over the two designated timepoints. This process was repeated in triplicate.

To assess therapeutic efficacy, CNV was induced by laser photocoagulation in 10 Brown Norway rats (Figure 1). Intravitreal injections of RO-634 or aflibercept were administered immediately following the injury and seven days later. Balanced salt solution (BSS) was used as a control. Fourteen days post laser injury, the eyes were harvested and CNV area was measured using masked analysis with a computer-assisted imaging program. Statistical analysis was performed using f-test and one-way ANOVA.

Results:
Wound analysis was completed at 12 hours post exposure to 40 ng of VEGF-A and the therapeutic agent. Compared to no treatment, HUVEC cells exposed to VEGF-A and aflibercept demonstrated a 70% reduction in migration, VEGF-A and bevacizumab demonstrated a 22% reduction in migration, VEGF-A and RO-634 demonstrated a 68% reduction in migration. The difference in reduction in VEGF-induced HUVEC migration between aflibercept and RO-634 was insignificant (p=0.93). The results are shown in Figure 2.

In the laser CNV model, the reduction in total area of CNV was 60% in RO-634 treated eyes and 53% in aflibercept treated eyes compared to BSS control (p=.0015, one-way ANOVA). RO-634 was found to be statistically superior to aflibercept in this study (p=.028).

Conclusion:
RO-634 appears to be effective in prevention of HUVEC migration post exposure to VEGF-A and is superior at preventing cell migration when compared with bevacizumab in this experiment. RO-634 was also associated with superior reduction of CNV compared to aflibercept. RO-634 demonstrates therapeutic efficacy

in early studies and should be further validated for treatment of retinal disease.

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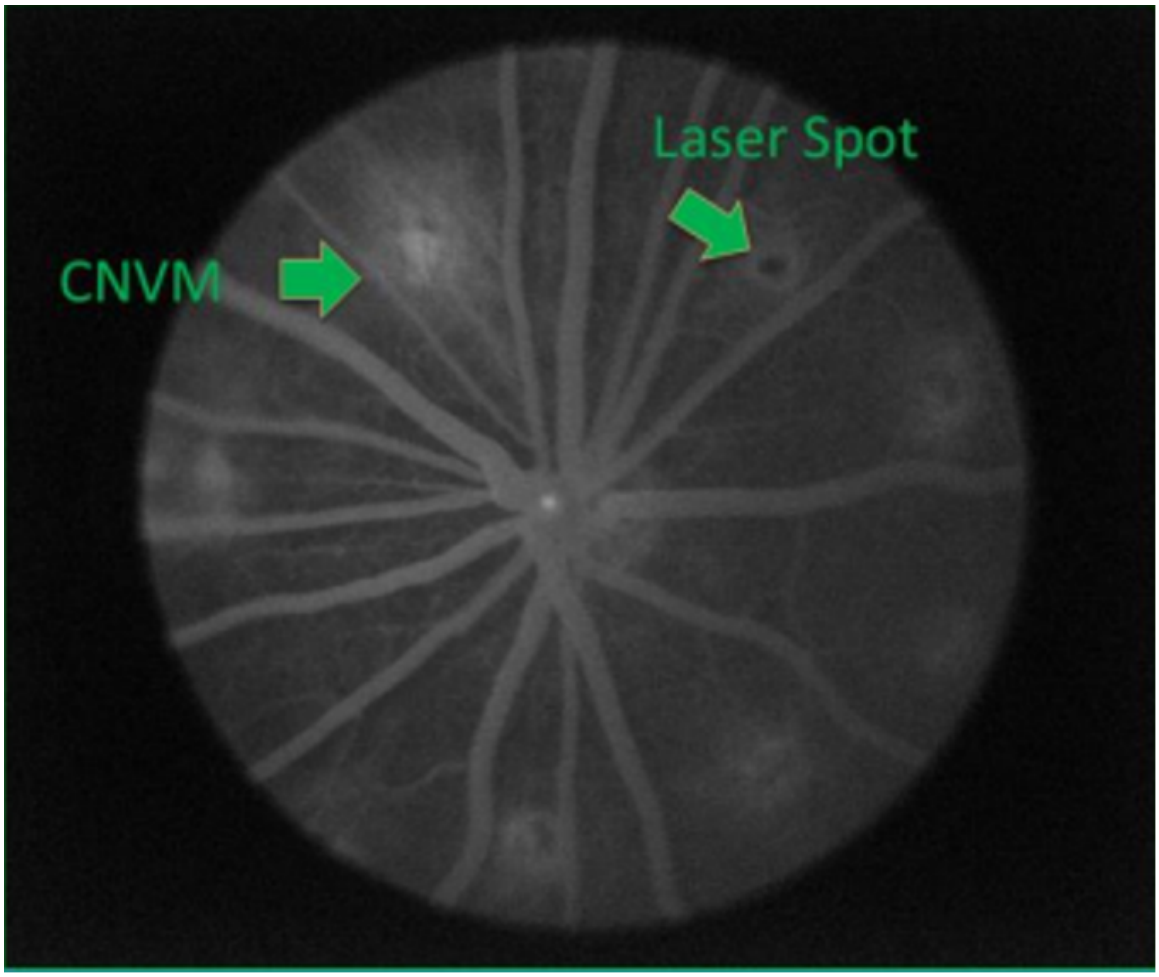

Figure 1: Laser induced CNV in rat model

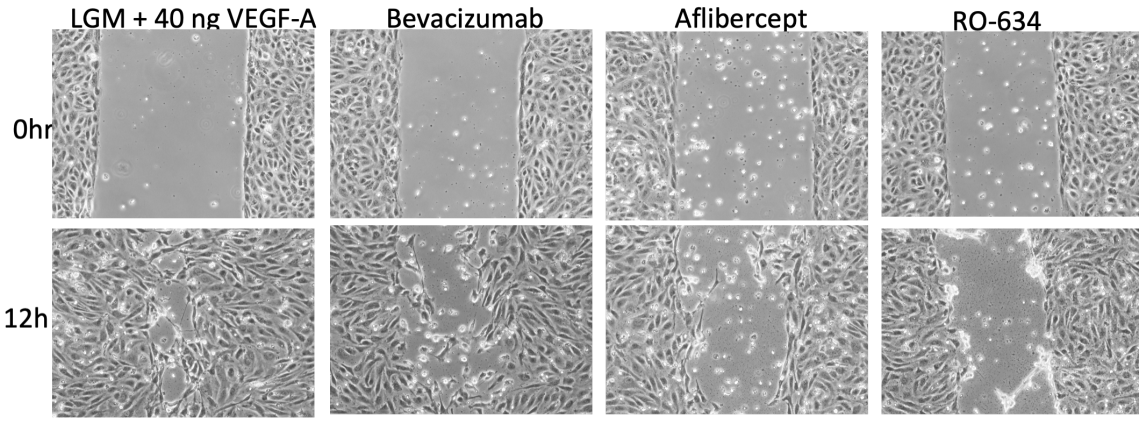

Figure 2: Wound closure after VEGF-A: Bevacizumab, Aflibercept, or RO-634

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Noninferiority of 1.7% Povidone–Iodine for Endophthalmitis Prophylaxis After Intravitreal Injections Compared With 5% Povidone–Iodine in an Office Setting

- Kamal Kishore, MD, MBBS
- Kurt Hanebrink

Objective:
Does 1.7% povidone-iodine solution, prepared by mixing commercially available 5% povidone-iodine solution with buffered saline solution in 1:2 ratio provide adequate prophylaxis against endophthalmitis after intravitreal injections?

Purpose:
5% povidone-iodine (PI) solution containing 0.5% elemental or "free" iodine, is recommended for post intravitreal endophthalmitis (PIE) prophylaxis (Avery 2014), but it is toxic to the ocular surface resulting in significant discomfort after intravitreal injections. Dilution of PI solution has shown more rapid killing of S aureus and M chelonei compared to 10% stock solution up to 1:100 dilution (0.1%) most likely due to increased availability of free iodine with dilution (Berkelman 1982). Personal experience with different concentrations of PI showed that 1.7% povidone-iodine solution was the highest concentration that was only minimally irritant to the eye. Therefore, 1.7% PI solution was used in 5499 consecutive intravitreal injections to assess its efficacy in preventing PIE.

Methods:
Retrospective noncomparative chart review of 5499 consecutive intravitreal injections (IVI) performed in 2021 at a single center who received 1.7% PI for PIE prophylaxis in an office setting. Disinfection technique involved instillation of 1 drop of 1.7% PI after OCT (or workup for injection only), prior to prepping the eyelids and lashes with 10% PI swabs, prior to IVI, and after the injection (a total of 4 drops). Sterile solid-blade lid speculum, conjunctival displacement, oblique entry, and reflux prevention by application of pressure at the injection site for 10 seconds with a sterile instrument were used in all cases. Gloves and drapes were not used but masks were worn by all personnel in the exam room. Rinsing of PI after IVI was not performed. Eye patch was not used except for Ozurdex. Results were compared with 34,130 IVI performed between 2011 and 2020 using 5% PI solution. Cases of PIE were identified by reviewing the surgical log.

Results:
No cases of PIE occurred in 2021 after 5499 injections. Injections consisted of intravitreal dexamethasone implant (16), bevacizumab (2590), and aflibercept (2893). Two cases of PIE were observed between 2011 and 2020 after 34,130 injections (one Coagulase negative staph, one S aureus). The incidence of PIE with 1.7% PI (0 in 5499) compares favorably with generally accepted incidence of 1 PIE per 2500 injections (McCannel 2011, Reibaldi 2018). All patients reported significantly less irritation and discomfort with 1.7% PI compared to 5% PI.

Conclusion:
1.7% PI provides effective prophylaxis against PIE. Caveats. 1. Prolonged contact time of ocular surface with PI (ASCRS, ESCRS, and AAO recommend 3 min contact time prior to cataract surgery. One study showed 15 min contact time for the complete killing of S epidermidis (Hosseini H, 2012)) 2. Multiple applications of dilute PI as reservoir of iodine may diminish due to dilution 3. Sterile speculum, conjunctival displacement, oblique entry and reflux prevention by application of pressure should be practiced. 3. Rinsing of the eye after injection should be avoided, as the needle site may not seal immediately allowing bacteria to enter the eye.

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Wet AMD 3 Symposium

Endophthalmitis After Intravitreal Injections with 0.05% Aqueous Chlorhexidine vs 5% Povidone-Iodine as Ocular Antiseptics

- Murtaza Adam, MD
- Sao Ton, MS

Objective:
What are the rates and outcomes of endophthalmitis following intravitreal injections of anti-vascular endothelial growth factor agents with 0.05% aqueous chlorhexidine versus 5% povidone-iodine as ocular antiseptics?

Purpose:
Topical Povidone-Iodine (PI) is a widely used ocular surface antiseptic for intravitreal injections and is associated with significant ocular discomfort in some patients. In limited studies, aqueous chlorhexidine (CHX), as an alternative antimicrobial to PI, has been associated with a low post-injection endophthalmitis (PIE) rate and less ocular discomfort compared to PI. This study compares the rates and outcomes of PIE for patients pre-treated with 5% PI and 0.05% CHX.

Methods:
This was a retrospective, single center, comparative cohort study of patients receiving intravitreal anti-VEGF injections from January 1, 2019, to November 30, 2021. Injection preparation with PI or CHX and cases of PIE were compiled using electronic health records and billing code data. The primary outcomes were the rate of endophthalmitis, culture results, and visual acuity. LogMAR visual acuity was determined at the time of causative anti-VEGF injection, endophthalmitis presentation, and 3-month follow-up.

Results:
A total of 68,334 intravitreal injections were administered by 13 retinal specialists during the study period. 13 of 33,064 (0.0393%; 1 in 2,543 injections) cases of presumed endophthalmitis occurred in the PI group, and 9 of 35,270 (0.0255%; 1 in 3,918 injections) cases in the CHX group (OR=0.65; 95% CI 0.27–1.52; p=0.319; Table 1). For the PI group, there were 2 culture-positive endophthalmitis cases (0.00605%, 1 in 16,532), compared to 2 cases in the CHX group (0.00567%, 1 in 17,635) (OR=0.94; 95% CI 0.13–6.66; p=0.949; Table 1). No significant difference was observed in visual acuity between PI and CHX at causative injection (p=0.41), endophthalmitis encounter (p=0.45), and 3-month follow-up (p=0.45; Table 2).

Conclusion:
There was no significant difference in the rate of PIE and visual acuity outcomes in the CHX group compared to the PI group. Further multicenter studies are needed to further evaluate the efficacy and safety of CHX compared to PI for intravitreal injection preparation.

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	Injections prepped with Povidone-Iodine (N = 33,064)	Injections prepped with Chlorhexidine (N = 35,270)	Odds ratio (95% CI)	P-value
Presumed endophthalmitis, N (%)	13 (0.0393%) 1 in 2,543 injections	9 (0.0255%) 1 in 3,918 injections	0.65 (0.27 – 1.52)	0.319
Culture-positive endophthalmitis, N (%)	2 (0.00605%) 1 in 16,532 injections	2 (0.00567%) 1 in 17,635 injections	0.94 (0.13 – 6.66)	0.949

N = number; CI = confidence interval

Table 1

	Povidone-Iodine Group (N=11)	Chlorhexidine Group (N=8)	P-value
Mean (SD) logMAR visual acuity at causative injection	0.49 (0.56)	0.72 (0.67)	0.41
Mean (SD) logMAR visual acuity at endophthalmitis presentation	1.71 (0.80)	1.42 (0.86)	0.45
Mean (SD) logMAR visual acuity at 3 months	0.80 (0.80)	1.09 (0.81)	0.45

N = number; SD = standard deviation; logMAR = logarithm of the minimum angle of resolution

Table 2