Silicone Droplets are Released by Syringes and Found in the Vitreous

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OBJECTIVE The majority of the commercially available syringes release silicone oil droplets, especially after agitation, and those droplets can be found in the vitreous of most patients.

PURPOSE Silicone oil droplets have been found in the vitreous of many subjects submitted to routine intravitreal injection. This study investigates the release of silicone oil by different models of syringe tested at multiple conditions, and the frequency of droplets apparent at clinical examination.

METHODS Eight models of syringe were analyzed for the release of silicone oil: USA- Terumo, BD Tuberculin, BD Luer-lok, BD Ultrafine, and Exel Insulin; Germany- Braun Omnifix-F, and Braun Injekt-F; Spain- BD Plastipak. The impact of air, priming, agitation and temperature of the fluid was assessed by light microscopy. Fourier transform infrared spectrocopy (FTIR) was used to identify the molecule. Additionally, a cross-sectional, comparative study was carried out in subjects undergoing routine intravitreal injection and controls in order to detect silicone oil in the vitreous by slit-lamp examination and ultrasonography. ImageJ was used to measure the index of silicone oil (IOS) in the vitreous.

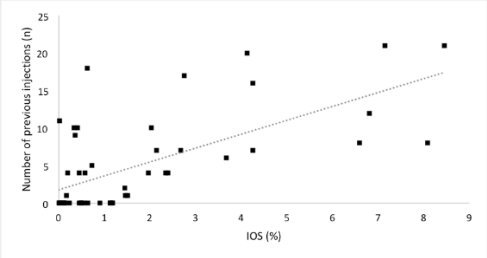
RESULTS Five hundred and sixty syringes were analyzed. Terumo 0.5 mL and BD Ultrafine 0.3 mL released more silicone oil. BD Tuberculin 1 mL, BD Luer-lok 1 mL, Exel 0.3 mL, BD Plastipak, Braun Omnifix-F 1 mL and Braun Injekt-F 1 mL released very little silicone oil. Priming the syringe, the presence of air, and different temperatures had no significant effect. On the other hand, agitation by flicking caused a significantly higher proportion of samples to be positive for silicone oil as well as in the number of droplets. FTIR showed polysiloxane in all syringes, except in Injekt-F. The clinical study included 30 controls vs. 37 previously treated eyes. Slit-lamp examination and ultrasonography, respectively, found silicone oil droplets in 68% and 76% of treated eyes and in 0% and 3% of controls. Treated eyes showed a higher IOS (2.7±2.6%) than controls (0.4±0.4%, P=0.0006), with IOS correlated with the number of prior intravitreal injections (Spearman's correlation test, .61; P<0.0001).

CONCLUSION Syringes are more likely to release silicone oil when agitated by flicking. Silicone oil droplets were found in most eyes previously subjected to intravitreal injection. The higher the number of injections, the greater the likelihood of finding silicone oil as well as an increased amount. Improved injection technique and syringes that release less silicone oil are warranted.

	Adjusted OR (CI 95%)	p
Condition (ref.= Fluid only)		
Postive control	16,690.65 (768.97 - 362,273.40)	<0.001
Priming + fluid + air	1.15 (0.41 - 3.22)	0.793
Fluid + flick	20.33 (6.89 - 59.99)	<0.001
Fluid + air + flick	86.58 (26.34 - 284.53)	<0.001
Priming + fluid + air + flick	61.28 (19.13 - 196.34)	<0.001
Priming + fluid (8° C) + air + flick	61.28 (19.13 - 196.34)	<0.001
Syringe (ref.=Injekt-F)		
Terumo	2,861.94 (487.06 - 16,816.44)	<0.001
BD Ultrafine	455.51 (98.28 - 2,111.18)	<0.001
BD Plastipak	45.56 (12.08 - 171.83)	<0.001
Omnifix-F	92.19 (22.84 - 372.15)	<0.001
BD Luer-Lok	92.19 (22.84 - 372.15)	<0.001
Exel	4.78 (1.32 - 17.33)	0.017
BD Tuberculin	5.37 (1.49 - 19.32)	0.010

N= 560.
OR: Priming + fluid + air = OR: Priming + fluid + air + flick (p< 0.001).
OR: Fluid + flick = OR: Fluid + air + flick (p=0.003).
OR: Priming + fluid + air + flick = OR: Priming + fluid (8o C) + air + flick (p=1.000).
OR: Exel = OR: BD Tuberculin (p=0.810).
OR: Omnifix-F = OR: BD Luer-Lok = OR: BD Plastipak (=0.310).

Table shows that flick is associated with higher OR than groups without flick. Additionally, when using oil-free Injekt-F as a reference, Terumo and BD Ultrafine syringes were associated with a greater chance of having silicone oil whereas Exel and BD Tuberculin with a lower chance.



ImageJ measures in both treated and control eyes showing that the greater the number of previous injections, the greater the index of silicone oil (IOS), which can be understood as a greater amount of oil.

HUMAN RESEARCH Yes: Approved by institutional review board

Differences in Intravitreal Silicone Oil Following Multiple Bevacizumab, Ranibizumab, and Aflibercept Injections

- John T. Thompson, MD

OBJECTIVE To compare the incidence of silicone oil microdroplets in the vitreous of eyes with 6 or more intravitreal injections of the same anti-VEGF drug.

PURPOSE There is increasing awareness of silicone oil microdroplets in patients receiving numerous intravitreal anti-VEGF injections.

METHODS This was a prospective cross-sectional study of 197 consecutive eyes receiving one of three anti-VEGF drugs for treatment of choroidal neovascularization, diabetic macular edema or macular edema from venous occlusive disease. All treatments in the study eye had to be with the same drug. The control group was 94 fellow eyes with no prior intravitreal injections. The anterior and mid-vitreous were carefully examined by slit lamp biomicroscopy at 12x to 16x with dilated pupil and ocular saccades to detect one or more silicone droplets in the vitreous. Silicone oil droplets were graded on a scale from 0 if absent to 4+ if present, based on number and size of droplets.

RESULTS The 3 anti-VEGF drugs were delivered with different syringes (bevacizumab in 0.3 ml BD polypropylene insulin syringes, ranibizumab in 1.0 ml BD polypropylene tuberculin syringes or the ranibizumab prefilled syringe and aflibercept in 1.0 ml BD polycarbonate syringes). The number of treatments were similar. Silicone microdroplets were detected in 39/54 eyes (72.2%) receiving bevacizumab, 14/90 eyes (15.6%) receiving ranibizumab and 26/53 eyes (49.1%) receiving aflibercept. No silicone oil microdroplets were found in 94 control eyes or a subset of 14 eyes treated only with ranibizumab prefilled syringes. The difference in silicone microdroplets incidence was significant when comparing bevacizumab to ranibizumab, aflibercept and controls (P<.001). The mean silicone oil microdroplets severity was 1.46 with

bevacizumab, 0.09 with ranibizumab and 0.36 with aflibercept (P<.001). Most patients were asymptomatic except in eyes with 2+ to 4+ silicone oil microdroplets.

CONCLUSION Silicone microdroplets in eyes receiving multiple bevacizumab, ranibizumab and aflibercept injections are more common than previously reported and differed between the three drugs. Intravitreal injections should be given using silicone free syringes and the use of BD insulin syringes to deliver bevacizumab should be abandoned due to the high incidence and severity of silicone oil microdroplets.

HUMAN RESEARCH Yes: Approved by institutional review board

What Does the HARBOR Data Reveal About the Relationship Between the Drying of Subretinal and Intraretinal Fluid and Associated Vision Outcomes?

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- Lauren Hill, BA, MS
- Ming Yang, PhD
- Shamika Gune, MD

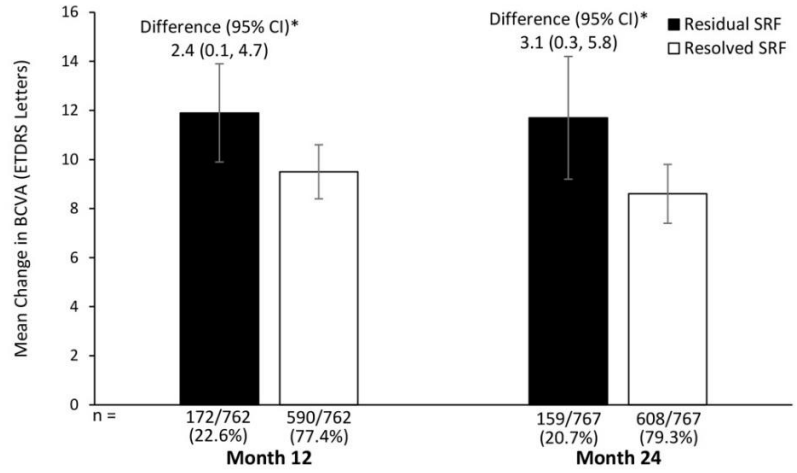
OBJECTIVE To investigate the impact of residual subretinal fluid (SRF) or intraretinal fluid (IRF) on vision outcomes in eyes receiving intravitreal ranibizumab for neovascular AMD (nAMD).

PURPOSE To evaluate the relationship between residual SRF or IRF and best-corrected visual acuity (BCVA) in a post-hoc analysis of patients with nAMD treated with ranibizumab over 24 months (HARBOR study; NCT00891735).

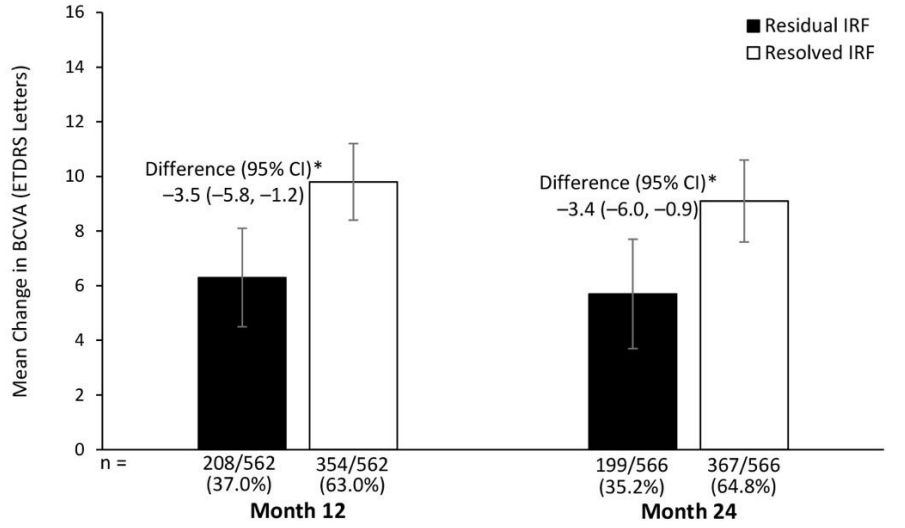
METHODS Treatment-naïve patients with nAMD were randomized to ranibizumab 0.5 mg or 2.0 mg administered monthly or PRN. This analysis included eyes with SRF and/or IRF at baseline (defined as screening, baseline, or week 1) and SD-OCT data at month 12 (M12)/M24 visit; all treatment arms pooled. Analysis outcomes were baseline BCVA, change from baseline in BCVA, and BCVA ≥69 letters (on the Early Treatment Diabetic Retinopathy Study [ETDRS] scale; Snellen equivalent: 20/40 or better) in the study eye at follow-up visits. Outcomes were evaluated independently for SRF and IRF status. All post baseline analyses were adjusted for baseline BCVA.

RESULTS At baseline, 86% and 63% of eyes had SRF or IRF, respectively. Mean baseline BCVA (letters, 95% confidence interval [CI]) was higher in eyes with residual SRF at M12 (58.8; 57.2, 60.4) and M24 (59.3; 57.8, 60.8) versus resolved SRF at M12 (53.5; 52.4, 54.5) and M24 (53.5; 52.5, 54.5). Adjusted mean change in BCVA from baseline was significantly greater at M12 and M24 in eyes with residual versus resolved SRF (Fig 1). The odds of achieving BCVA ≥69 letters for eyes with residual versus resolved SRF were similar at M12 (odds ratio: 1.07; 95% CI: 0.72, 1.59) and M24 (1.14; 0.77, 1.68). In contrast, adjusted mean change in BCVA was significantly worse at M12 and M24 in eyes with residual versus resolved IRF (Fig 2). There was a trend toward lower visual gains when IRF was in the central region (mean difference: M12, −4.2 letters [−8.5, 0.1]; M24, −3.4 letters [−8.1, 1.3]) or severe versus mild (M12, −4.1 letters [0.6, −8.8]; M24, −4.5 letters [1.9, −10.9]).

CONCLUSION Vision gains were higher in eyes with residual SRF versus resolved SRF; in contrast, vision gains were lower in eyes with residual IRF. These results suggest that further investigation is needed to define the optimal fluid outcomes needed for maximizing long-term vision outcomes in nAMD and to understand the relationship between SRF, IRF, and the integrity of various retinal layers.



Mean change in BCVA in eyes with nAMD with resolved versus residual SRF after intravitreal ranibizumab treatment. *Adjusted for baseline BCVA. SRF, subretinal fluid.



Mean change in BCVA in eyes with nAMD with resolved versus residual IRF after intravitreal ranibizumab treatment. *Adjusted for baseline BCVA. IRF, intraretinal fluid.

HUMAN RESEARCH Yes: Approved by institutional review board

Higher-Order Optical Coherence Tomography Fluid Burden Assessment: Analysis From the OSPREY Trial

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- Natalia Albuquerque Lucena Figueiredo, MD
- Leina Lunasco
- Jamie Reese, RN
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OBJECTIVE This higher-order OCT analysis of the OSPREY trial will provide information on the rate of anatomic response and fluid burden dynamics following brolucizumab therapy for nAMD.

PURPOSE Current conventional OCT metrics are limited, but higher-order OCT assessment enables in-depth evaluation of Spectral Domain-OCT (SD-OCT) imaging biomarkers for therapeutic effect. This analysis evaluated the fluid burden metrics in the OSPREY phase II trial for neovascular age-related macular degeneration (nAMD) following treatment with brolucizumab or aflibercept.

METHODS The OSPREY trial is a phase II randomized, double-masked, active-controlled study of 56 weeks' duration comparing brolucizumab to aflibercept in nAMD. Subjects were randomized 1:1 to brolucizumab 6 mg or aflibercept 2 mg, both at q8w dosing through Week 40 after 3 monthly loading doses. The final cycle was extended in the brolucizumab group for assessment of q12w dosing, with the aflibercept group maintained on q8w dosing (56 weeks). Macular cube scans were uploaded into a novel analysis software platform, and volume and area of macular fluid were quantified using an advanced-analysis algorithm.

RESULTS The matched phase (Weeks 0, 4, 8, 12, and 16) and extended phase of the trial (Weeks 32, 36, 40, 44, 48, 52, and 56) were selected for higher-order OCT analysis. The higher-order analysis of the matched phase will provide information on the rate and extent of fluid resolution and differential responses. The analysis of the extended phase will identify eyes that perform optimally to q12w dosing with brolucizumab, as well as eyes at risk for fluid rebound with extended interval dosing. Baseline features that may be predictive of tolerance at various treatment intervals will be evaluated.

CONCLUSION Following anti-VEGF therapy for nAMD, varying degrees of fluid frequently persist. In this study, a novel OCT analysis approach enabled volumetric characterization of macular fluid allowing for a unique assessment of persistent fluid and providing opportunities for identification of imaging biomarkers that may predict optimal response to therapeutics, best dosing regimens and overall prognosis.

HUMAN RESEARCH Yes: Approved by institutional review board

Biweekly Anti-VEGF Dosing for Chronic Refractory Neovascular Age-Related Macular Degeneration Unresponsive to Standard Monthly Dosing

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- Brandon G. Busbee, MD

OBJECTIVE To assess the safety and efficacy of biweekly anti-VEGF dosing in patients with refractory neovascular age-related macular degeneration (NVAMD).

PURPOSE Despite long-term monthly anti-VEGF therapy, intra- (IRF) and/or subretinal fluid (SRF) persists in a subset of eyes affected by NVAMD. Currently, anti-VEGF agents may not be used any more frequently than every 28 days despite pharmacokinetic and OCT angiographic data suggesting a peak effect at 2-3 weeks post-injection. This study assesses the outcome of biweekly dosing for refractory NVAMD.

METHODS A retrospective analysis of 18 consecutive patients with NVAMD-related refractory IRF and/or SRF on OCT was performed. “Refractory” patients underwent ≥6 months of anti-VEGF therapy (mean: 35.5 mos) administered at mean interval of 30.9 days. Included patients received at least five consecutive biweekly anti-VEGF doses, defined as an injection followed by a subsequent injection within 14 (±7) days. Snellen vision, OCT thickness parameters, and safety data were collected for all visits beginning with the baseline visit (first biweekly treatment) through the first ≥28 day follow-up visit. The primary endpoint was OCT central subfield thickness (CST) after the 5th biweekly injection (visit 5).

RESULTS Included patients underwent a mean of 18.1 biweekly anti-VEGF injections at a mean interval of 16.5 days. Mean CST improved significantly from baseline (333.6um) to visit 5 (281.0um, p=0.006). This improvement was sustained through the end of the biweekly dosing (283.6um, p=0.004) but was not sustained upon returning to monthly dosing (291.7um, p=0.379). Significant improvement was also noted in cube volume and average cube thickness at visit 5, and these improvements were sustained upon return to monthly dosing. Overall, complete resolution of fluid was noted in 16.7% and 27.8% of patients at visit 5 and the final biweekly visit, respectively. Sixteen patients had baseline SRF, which resolved in 31.2% and 37.5% at visit 5 and the final biweekly visit, respectively. Baseline IRF (n=5 patients) was less responsive to treatment. Visual acuity improved significantly from 20/82 at baseline to 20/47 at visit 5 (p=0.013) though this was not sustained. There were no cases of endophthalmitis.

CONCLUSION Increasing the frequency of anti-VEGF dosing led to significant reduction in refractory NVAMD-related IRF and SRF with improvement in visual acuity after five biweekly doses. Given the heterogeneity of anti-VEGF agent used, follow-up timing, and treatment duration in this retrospective analysis; a prospective study of biweekly dosing in this difficult-to-treat population would be valuable.

HUMAN RESEARCH Yes: Exempt from approval

Open-Label Study Evaluating the Effects of the CCR3 Antagonist ALK4290 in Patients With Neovascular AMD Refractory to Anti-VEGF Therapy

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- Elizabeth Jeffords
- Vicki Klutzaritz
- Esther Rawner, MD
- Erin Newman

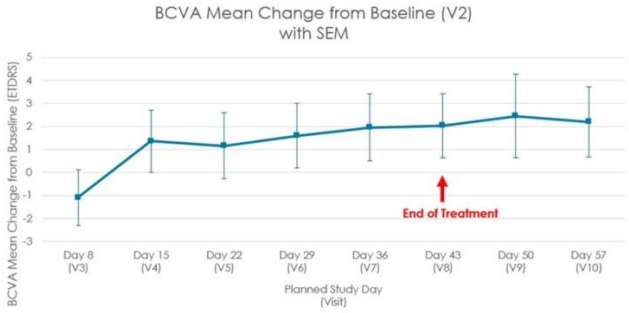
OBJECTIVE To investigate the safety and therapeutic effects of oral dosing with ALK4290 (C-C chemokine receptor type 3 (CCR3) antagonist) for 6 weeks in patients with nAMD refractory to anti-VEGF therapy.

PURPOSE Current standard of care for nAMD consists of intravitreal anti-VEGF therapy but these treatments can be costly or burdensome and may lead to suboptimal treatment. For the subset of nAMD patients who are refractory to anti-VEGF drugs, treatment choices are particularly limited. This study explored the safety and efficacy of an oral C-C chemokine receptor type 3 (CCR3) antagonist in these patients.

METHODS This open label, prospective Phase 2a study enrolled patients who were at least 50 years old and had active, refractory nAMD. Eligible patients had received at least 3 consecutive anti-VEGF injections with their last injection between 30 and 90 days prior to the screening visit, had persistent subretinal and/or intraretinal fluid, and absence of improvement of BCVA. ALK4290 400 mg tablets were administered twice daily by mouth for 6 weeks. Study endpoints included safety and tolerability, ETDRS BCVA assessment, and morphological measurements with SD-OCT and fundus photography/fluorescein angiography (FA). Additional exploratory biomarker analyses were performed.

RESULTS A total of 25 evaluable subjects, with a mean age of 76 years, completed the study (6 weeks of dosing with 2 additional weeks of follow-up). At baseline, the evaluable subjects had a mean BCVA of 53.4 letters with a mean disease duration of 1.9 years. In this refractory population, mean improvement in BCVA was +2.0 letters at the end of the 6-week treatment period (Graph 1). Eighteen subjects (72%) either improved or maintained their vision (3 0 letters change from baseline), 10 (40%) had a 3 5 letter gain, and 2 (8%) had a 3 10 letter gain. In the subset of subjects that gained 3 5 letters, the mean change in BCVA was +7.7 letters (Table 1). There were no severe or serious adverse events, and no adverse events led to discontinuation of the study drug.

CONCLUSION In this cohort of refractory nAMD patients, oral ALK4290 was found to be safe and well-tolerated with benefits to BCVA. These early results suggest potential efficacy of ALK4290 as an oral treatment for nAMD. An effective and safe oral agent that augments standard of care for non-responsive patients would address an important unmet need. Follow-on placebo-controlled studies are planned.



Mean changes in best corrected visual acuity from baseline are shown over the duration of the study and the 2-week post-treatment observation period.

BCVA Change from Baseline (at 6 weeks)	
N	25
>10 letters	2 (8%)
≥ 5 Letters	10 (40%)
< 5 to ≥ 0 Letters	8 (32%)
< 0 Letters	7 (28%)
≥ 0 Letters	18 (72%)
Mean Change (Median)	+2.0 (+2)
Mean Change (Median) "Responders" (≥ 5 Letters)	+7.7 (+7.5)

The proportions of patients with changes in mean best corrected visual acuity over several important ranges are shown.

HUMAN RESEARCH Yes: Approved by institutional review board

FIDO Study: 10-Year Outcomes of Eyes Receiving Continuous, Fixed-Interval Dosing of Anti-VEGF Agents for Neovascular Age-Related Macular Degeneration

- Ivan J. Suner, MD, MBA
- Marc C. Peden, MD

OBJECTIVE Does long-term, continuous, fixed-interval dosing with anti-VEGF agents maintain early visual acuity gains in patients with neovascular age-related macular degeneration?

PURPOSE To report the 10-year visual acuity outcomes of our cohort of patients receiving continuous, fixed-interval dosing of Anti-VEGF agents for neovascular age-related macular degeneration.

METHODS Retrospective, single center (Retina Associates of Florida) consecutive case series of patients receiving continuous, fixed-interval dosing (every 4-8 weeks) of anti-VEGF agents (ranibizumab, aflibercept, and/or bevacizumab) for 10 years. Changes from baseline were calculated at yearly intervals.The primary outcome measure was mean change in ETDRS letter score (converted from Snellen acuity); secondary outcome measures included the percentage of patients with ≥ 20/40 vision, percentage of patients with improvement from baseline, percentage of patients with loss ≥ 3 lines of visual acuity from baseline. Rates of anti-VEGF switch, IOP elevation, and endophthalmitis are also reported.

RESULTS 130 eyes of 116 patients with continuous, fixed-interval dosing beginning in 2016-2018 were identified. The main reasons for dropout from the study cohort were death or moving away from the practice area. Seasonal patients (snowbirds) with irregular injection intervals were not included in the analysis.

The mean change in letter score at year 2 was +19 letters, and was relatively well-maintained at year 10 at +14 letters from baseline. Patients received a mean of 10 injections per year for the 10-year study period.

Driving vision (20/40 or better) was achieved in 45% of eyes at 10 years, compared to 3% of eyes at baseline.

At 10 years, vision improved from baseline in 70% of eyes, and declined by ≥ 3 ines in 6% of eyes.

CONCLUSION This is the largest dataset of consecutive patients receiving continuous, fixed-interval dosing with anti-VEGF agents for neovascular AMD for 10 years. The results demonstrate favorable long-term preservation of early visual acuity gains out to 10 years. This suggests that there is a greater risk of vision loss by undertreatment than by continuous treatment with anti-VEGF agents.

HUMAN RESEARCH Yes: Exempt from approval

Geographic Atrophy in the Canadian Treat and Extend Trial With Ranibizumab in nAMD Patients: CANTREAT Study 24-Month

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- Tom Sheidow, MD, FRCS(C)
- R. Geoff Williams, MD, FRCS(C)
- Mark D.J. Greve, MD, FRCS(C)
- John Galic, MD, FRCS(C)
- Marcel Lahaie, B.A.A.

OBJECTIVE This study aimed to assess non-inferiority of ranibizumab using treat-and-extend (T&E) versus once-monthly (OM) dosing in neovascular age-related macular degeneration (nAMD) patients over 36 months.

PURPOSE Several studies have suggested that anti-VEGF therapy promotes geographic atrophy in nAMD. Few large clinical studies have evaluated the extent of geographic atrophy resulting from a T&E ranibizumab dosing regimen compared to a OM dosing regimen in nAMD; this study does so in a subset of patients.

METHODS This prospective, randomized, open-label, multicenter, post-authorization non-inferiority study randomized patients 1:1 to T&E or OM after being prescribed ranibizumab. Eyes with significant centre-involving geographic atrophy at baseline were excluded. At sites with autofluorescence imaging, investigators descriptively categorized changes in the area of geographic atrophy at Months 12 and 24 compared to Baseline and Month 24 compared to Month 12. This analysis describes baseline characteristics for all patients and changes in geographic atrophy in a patient subset. Visual acuity and non-inferiority were previously reported. Ethics boards at all active sites and an IRB approved the study.

RESULTS There were 580 patients (287 T&E: 293 OM) randomized and 80% (462 [236 T&E: 226 OM]) completed 24 months of follow-up. Most were Caucasian (94%) and female (60%) and mean age (SD) was 78.8 (7.8) years. There were 162/580 (28%) patients with reported autofluorescence data at 9 of the 27 participating sites. Between Baseline and Month 12, the majority had geographic atrophy categorized as unchanged (47 [59%] OM: 50 [61%] T&E) followed by minimally increased (17 [21%] OM: 16 [20%] T&E) and minimally decreased (12 [15%] OM: 8 [10%] T&E). Similarly, between Baseline and Month 24 most were unchanged (46 [58%] OM: 41 [51%] T&E) followed by minimally increased (22 [28%] OM: 15 [19%] T&E), while 17 (22%) T&E and 7 (9%) OM patients were much increased. From Month 12 to 24, most patients were unchanged (56 [70%] OM: 51 [63%] T&E) and 21 (26%) T&E and 21 (26%) OM were minimally increased. More precise quantitative measurements of the area of geographic atrophy over time are ongoing.

CONCLUSION These data suggest no clinically meaningful differences were observed between the T&E and OM groups. This analysis of nAMD patients treated with ranibizumab showed that those assessed for geographic atrophy were mostly unchanged between baseline and Month 12, baseline and Month 24, and between Month 12 to Month 24.

HUMAN RESEARCH Yes: Approved by institutional review board

First Results From a Phase 1B Multiple-Dose Study of KSI-301: A Novel Anti-VEGF Antibody Biopolymer Conjugate (ABC) With Extended Durability

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- Diana V. Do, MD
- Joel Naor
- Desiree Beutelspacher, BS
- Jason S. Ehrlich, MD , PhD
- Victor Perlroth, MD, MBA
- J. Pablo Velazquez-Martin, MD

OBJECTIVE Explore the Bioactivity, Safety, and Pharmacokinetics of Multiple Intravitreal Administrations of KSI-301, a Novel anti-VEGF Antibody Biopolymer Conjugate (ABC), in Subjects with wAMD, DME and RVO

PURPOSE Real world vision outcomes of anti-VEGF therapy are limited by the high treatment burden of existing agents. KSI-301 is a novel ABC that potently inhibits VEGF. Its design optimized both size and molar dose to improve intraocular durability. This phase 1b study is designed to evaluate bioactivity, safety, and pharmacokinetics of multiple intravitreal injections of KSI-301.

METHODS ABCs built with an optically-clear, phosphorylcholine biopolymer may optimize the intraocular half-life, retinal tissue bioavailability, potency, stability, and molar dose of intravitreally-delivered biologics. In phase 1a, eyes with DME received a single injection of KSI-301 (1.25 mg, 2.5 mg, or 5 mg) and were followed for 12 weeks. In the Phase 1b study, two

dose levels of KSI-301 (2.5 and 5 mg) are being assessed in treatment naïve subjects with wet AMD (~20 patients), DME (~20), and RVO (~10). Each subject will receive 3 initial injections of KSI-301, 4 weeks apart. Subjects are evaluated for the need for additional KSI-301 doses at 4 week intervals beginning at week 16.

RESULTS A Phase 1a single-ascending dose study previously demonstrated that a single intravitreal injection of KSI-301 in nine subjects with DME was safe and well tolerated. No drug-related adverse events, no intraocular inflammation, and no dose-limiting toxicities were observed. Rapid-onset, high-magnitude improvements in BCVA with corresponding reductions in macular thickness on OCT were observed at all dose levels. Of the 8 eyes that responded to the single dose, all had improvement from baseline at 12 weeks by BCVA, OCT, or both. These results provide a preliminary proof-of-concept for KSI-301's therapeutic role in retinal vascular diseases and for the antibody biopolymer conjugate approach. In this presentation, emerging results of the phase 1b multiple-dose study of KSI-301 in patients with wet AMD, DME, and RVO will be presented for the first time.

CONCLUSION Real-world treatment outcomes with anti-VEGF therapy are limited by a high treatment burden. ABCs have the potential to address this challenge. KSI-301 was safe, well-tolerated, and bioactive through 12 weeks in a single ascending dose Phase 1a study. Outcomes from the Phase 1b multiple-dose study in patients with treatment naïve wAMD, DME, and RVO will be presented for the first time.

HUMAN RESEARCH Yes: Approved by institutional review board

Port Delivery System With Ranibizumab (PDS): Key Outcomes From the Ladder Phase 2 Trial That Supported Archway Phase 3 Study Design in nAMD

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- Giulio Barteselli, MD
- Shamika Gune, MD

OBJECTIVE To present key results from the phase 2 Ladder trial of the Port Delivery System with ranibizumab (PDS) in patients (pts) with neovascular AMD (nAMD) that supported the phase 3 Archway study design.

PURPOSE The PDS is a refillable, indwelling implant providing diffusion-mediated continuous intravitreal (ITV) delivery of ranibizumab (RBZ) for treatment of nAMD. In this analysis, we evaluated how choroidal neovascular (CNV) lesions responded to treatment with the PDS in the phase 2 Ladder trial. We also specify how Ladder primary and secondary endpoint results informed Archway phase 3 study design.

METHODS The phase 2 Ladder trial (NCT02510794) was designed to evaluate the efficacy and safety of the PDS with 10, 40, and 100 mg/mL RBZ formulations compared with monthly ITV RBZ 0.5 mg injections for the treatment of nAMD. The primary analysis was conducted when the last enrolled pt completed the month (M) 9 visit. The primary endpoint was the time to first required implant refill. Secondary endpoints included change from baseline (BL) in best-corrected visual acuity (BCVA) and central foveal thickness (CFT), and safety. Fluorescein angiography imaging was performed on all pts at the BL, M4, M6, and M9 visits, and changes in CNV area on study and CNV lesion size were evaluated by masked graders.

RESULTS Ladder evaluated 220 pts in the primary analysis population randomized 3:3:3:2 to PDS 10, 40, and 100 mg/mL formulations or ITV RBZ 0.5 mg monthly. 63.5%, 71.3%, and 79.8% of pts did not meet refill criteria until ≥6 mo for the PDS 10, 40, and 100 mg/mL arms, respectively. Mean change in CNV area and CNV lesion size from BL to M6 were comparable between the PDS 100 mg/mL and ITV RBZ 0.5 mg arms, with a reduction in both mean CNV area and mean lesion size over time (Table). A dose response was observed in change in CNV area. Clear dose responses across primary and secondary endpoints were also observed in the PDS treatment arms, including time to first refill, mean BCVA change, and mean CFT change from BL at M9, with visual and anatomic outcomes for the PDS 100 mg/mL comparable to the ITV RBZ 0.5 mg arm from M3–M9. Ocular adverse event rates were slightly higher in the PDS arms in the month post surgery compared with ITV RBZ 0.5 mg arm, but were comparable during the follow-up period.

CONCLUSION In Ladder, 80% of pts in the PDS 100 mg/mL arm did not require an implant refill until ≥6 mo. Mean change from BL in BCVA, CFT, CNV area, and CNV lesion size were comparable between the PDS 100 mg/mL and monthly ITV RBZ arms at M6. The Ladder results support 24-week fixed refills in the ongoing phase 3 Archway trial (NCT03677934), which is currently enrolling.

	PDS Ranibizumab 10 mg/mL	PDS Ranibizumab 40 mg/mL	PDS Ranibizumab 100 mg/mL	Monthly Intravitreal Ranibizumab 0.5 mg
CNV area on study (mm^2)				
Mean at BL	2.485	2.225	2.197	2.280
Change from BL	0.511	0.362	–0.407	–0.484
Total CNV lesion size (mm^2)				
Mean at BL	2.912	3.408	3.131	3.025
Change from BL	0.567	–0.202	–0.870	–0.898

Table. Mean change in CNV area and total CNV lesion size at M6 as evaluated by fluorescein angiography in the PDS and RBZ treatment arms

HUMAN RESEARCH Yes: Approved by institutional review board

Interaction of Genotypes and AREDS Formulation Use in the Development of Neovascular AMD

- Pradeepa Yoganathan, MD, FRCS(C)
- Stephen R. Kaufman, MD

OBJECTIVE To investigate the reported interaction between genetic risk, treatment with Age-Related Eye Disease Study formulation (AREDS) and progression to neovascular age-related macular degeneration (nvAMD)

PURPOSE It has been reported that patients with high complement factor H (CFH) and low age-related maculopathy susceptibility 2 (ARMS2) risk alleles, i.e., Genotype Group 2 (GTG2), had increased risk of developing nvAMD following exposure to AREDS. This study determines whether pts with nvAMD exposed to AREDS are more likely to be in GTG2 as compared to other prespecified genotype groups.

METHODS We performed a masked cohort study of the interaction between 4 prespecified AMD genotype groups and AREDS use on the progression to nvAMD. The authors identified patients within their clinical practices with newly developed nvAMD. A survey was administered to those patients who could accurately report AREDS use or non-use prior to diagnosis of nvAMD. AREDS users were defined as those with prior intake of >5 years of at least 7 doses/week. AREDS non-users were defined as lifetime AREDS intake <1 month. Genotyping of masked cheek swab specimens were obtained on 199 pts with a reliable history of AREDS use. De-identified GTG and AREDS exposure was verified by an independent data collector.

RESULTS We compared the ratio of AREDS users vs. non-users for patients in 4 GTGs based on combinations of CFH and ARMS2 genotypes. Previous studies have demonstrated that certain

genotypes of CFH and ARMS2 are associated with a high risk of developing nvAMD and other genotypes of CFH and ARMS2 are associated with a low risk of nvAMD. GTG1 = low CFH and low ARMS2 risk; GTG2 = high CFH and low ARMS2 risk; GTG3 = low CFH and high ARMS2 risk; GTG4 = high CFH and high ARMS2 risk. GTG2 has been associated with an adverse response to AREDS treatment, while GTG3 has been associated with a beneficial response.The ratio of AREDS use to non-use for GTG2 was 13/22, or 0.59; for GTG3 it was 11/80 or 0.14; and for combined GTG1 plus GTG3 plus GTG4 it was 28/136 or 0.21. The odds ratio of GTG2 versus GTG3 was 4.2 with a Chi square p value of 0.0013. The odds ratio of GTG2 versus combined GTG1 plus GTG3 plus GTG4 was 2.8 with a chi-squared test p value of 0.0077.

CONCLUSION Patients in Genotype Group 2, i.e., high CFH and lows ARMS2 risk alleles, are more likely to develop nvAMD following exposure to routine AREDS formulation. These data support a genuine interaction between GTG2, AREDS use, and progression to nvAMD. Additional patients will be added to this analysis by the time of the 2019 ASRS Annual Meeting.

GTG	AREDS users	AREDS non-users	Odds: users/non-users
2	13	22	0.59
3	11	80	0.14
1,3 or 4	28	136	0.21
Odds Ratio GTG2 vs GTG3:		4.2	p = 0.0013
Odds Ratio GTG2 vs GTG 1, 3, and 4:		2.8	p = 0.0077

Genotype group 2 had significantly higher risk of developing nvAMD when exposed to AREDS as compared to other genotype groups

HUMAN RESEARCH Yes: Approved by institutional review board

The Average Patient Does Not Enter Your Office: What Can We Learn About Treating nAMD From Individual Patient Responses

- David S. Boyer, MD
- Anna M. Abolian, OD
- Bann-mo Day, PhD
- Ivaylo Stoilov, MD

OBJECTIVE To understand why some patients with nAMD achieve near normal vision with anti-VEGF treatment while others do not.

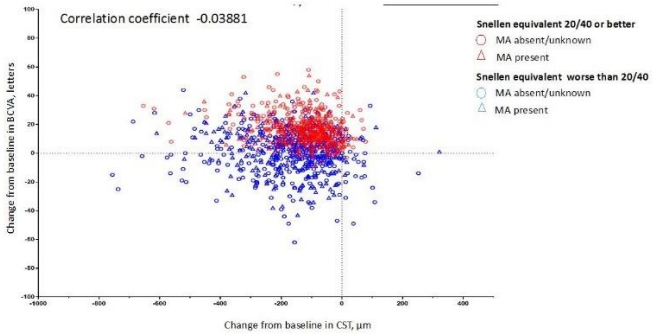
PURPOSE The primary endpoint for the anti-VEGF trials in nAMD is the mean change in BCVA from baseline. Examining the individual patients' responses reveals a complex picture, with some patients gaining vision, some maintaining, and others not doing very well. We analyzed the differences between patients who regained normal vision and those who remained visually impaired following anti-VEGF treatment.

METHODS HARBOR was a 24-month, phase 3, randomized, multicenter, double-masked trial of ranibizumab in treatment-naive nAMD. Patients (N = 1097) were randomized to receive ranibizumab 0.5 mg or 2.0 mg intravitreal injections administered monthly or on a PRN basis after 3 monthly loading doses. A "birds eye" view of the main treatment outcomes at month 24 was developed by plotting change from baseline in BCVA and CST by Snellen 20/40 or better, and presence of macular atrophy at month 24 for all patients, allowing for visual interpretation of the data. Correlation between anatomic and vision outcomes and differences between patients with 20/40 or better and worse than 20/40 vision were analyzed.

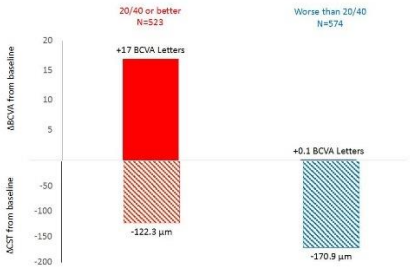
RESULTS There was no correlation between change in CST and change in BCVA (correlation, Figure 1) at month 24. Interestingly, some patients experienced significant reduction in CST, but

lost vision. Macular atrophy was observed in both patients with poor and good vision outcomes. Patients who had vision of 20/40 or better (n = 523) at month 24 on average gained a mean (±SD) of +17.0 (±10.4) BCVA letters and reduced CST by –122.3 (±99.9) µm. Patients with vision worse than 20/40 (n = 574) had greater reduction in CST by –170.9 (±140.2) µm. However, they gained only +0.1 (±15.2) letters (Figure 2). Presence of subretinal fluid (SRF) at day 7 (after first ranibizumab injection) was the strongest anatomic predictor for BCVA gain ≥15 letters at month 12. Eyes with SRF at baseline gained on average 10.3 versus 6.6 letters for eyes without SRF. At month 24, macular atrophy was detected in 33% of eyes without concurrent SRF and in only 8% of eyes with SRF.

CONCLUSION There was no correlation between reduction in CST and BCVA gain at month 24 in patients treated with ranibizumab. There was discord between CST reduction and BCVA gain above and below the 20/40 vision threshold, which highlights the importance of overall retina health. Presence of SRF at baseline concurrent with ranibizumab treatment was associated with better vision outcomes.



Scatterplot of change from baseline in BCVA and CST, Snellen 20/40 or better and presence of macular atrophy at month 24 (all trial participants; N = 1097)



Vision and anatomic outcomes in patients with and without visual disability at month 24

HUMAN RESEARCH Yes: Approved by institutional review board