Intravitreal Ranibizumab for Macular Edema Secondary to Central Retinal Vein Occlusion

Jessica Basefsky, Dante Pieramici, Robert Avery, Ma'an Nasir, Alessandro Castellarin, Melvin Rabena, Sarah Risard
California Retina Consultants and Research Foundation, Santa Barbara, California, USA

A350

INTRODUCTION

- Macular edema is a primary cause of visual loss in patients with central retinal vein occlusion (CRVO), a common retinal vascular disease.
- There is currently no proven therapy for the treatment of macular edema secondary to CRVO, representing an unmet clinical need.
- Vascular endothelial growth factor A (VEGF-A) increases retinal vascular permeability and may play a role in the development of macular edema.
  - VEGF-A levels are elevated in the ocular fluid of patients with diabetic retinopathy and CRVO,[1,2] as well as branch RVO (BRVO).[3]
  - VEGF-A inhibition decreases macular edema in patients with diabetic macular edema.[4]
  - VEGF-A may be a promising therapeutic target in macular edema associated with perfused CRVO.
- Ranibizumab (LUCENTIS®) is a humanized antigen-binding antibody fragment that targets all VEGF-A isoforms and their biologically active degradation products.
  - Ranibizumab is approved by the US Food and Drug Administration for the treatment of neovascular age-related macular degeneration.
  - Ranibizumab improved vision and decreased central retinal thickness (CRT) in 2 small studies (N = 10) of patients with diabetic macular edema,[5,6] as well as in patients with CRVO and BRVO (n = 20 each).[7]

OBJECTIVE

The purpose of this study is to evaluate the biologic effect, changes in visual acuity (VA), and safety of intravitreal (ITV) ranibizumab in patients with macular edema secondary to CRVO.

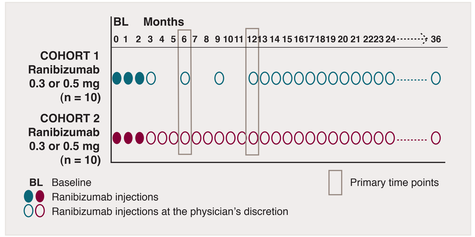
METHODS

- This is an ongoing, prospective, open-label study.
- A total of 20 patients with clinical, angiographic, and optical coherence tomography (OCT) evidence of macular edema secondary to CRVO were enrolled.
- Patients were randomized to 1 of 2 cohorts (Figure 1).
  - Cohort 1 (n = 10; randomized to receive 0.3 mg or 0.5 mg ranibizumab): 3 monthly ITV ranibizumab injections (at baseline, month 1, and month 2) followed by injections every 3 months as needed (PRN) until month 12, and then PRN every month until month 36
  - Cohort 2 (n = 10; randomized to receive 0.3 mg or 0.5 mg ranibizumab): 3 monthly ITV ranibizumab injections (at baseline, month 1, and month 2) followed by monthly PRN injections until month 36
- Central retinal vein caliber was measured using the image measurement feature of ANKA Systems, Inc. using color fundus photographs and fluorescein angiograms. All retinal veins were measured within 1 mm of the boundary of the optic nerve head and retina. The same veins were measured at the same location for follow-up evaluations. The extent of intraretinal hemorrhage was also measured from fundus photographs.
- During the first year of the study, cohort 1 patients were evaluated quarterly and cohort 2 patients were evaluated monthly.
- During the second and third years, all patients will be evaluated and treated PRN monthly.

Study Endpoints

- Primary endpoints
  - Percentage of patients gaining ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters of best-corrected VA (BCVA) from baseline to 6 and 12 months
- Secondary endpoints
  - Mean change in BCVA from baseline to 3, 6, 9, 12, 15, 18, 21, and 24 months
  - Percentage of patients losing ≥15 letters of BCVA from baseline to 3, 6, 9, 12, and 24 months
  - Mean change in CRT (as measured by OCT) from baseline to 3, 6, 9, 12, 15, 18, 21, and 24 months
  - Rate of progression to ischemic CRVO
  - Incidence and severity of ocular and nonocular adverse events (AEs)

Figure 1. Study design.



RESULTS

Study Patients

- Of the 20 patients enrolled, one patient in cohort 1 completed the first year according to protocol and withdrew from the study immediately after the month 12 study visit because she moved to another state.
- These results include 24-month data for cohort 1 and 12-month data for cohort 2.
- Mean number of injections at month 12: 5.7 (range 4-7) for cohort 1 and 8.1 (range 5-13) for cohort 2
- Mean number of injections between months 12 and 24 for cohort 1: 2.7 (range 0-6, maximum possible injections = 12)

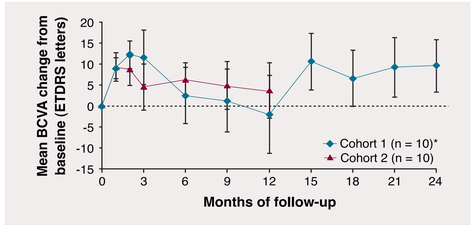
Table 1. Patient Demographics and Baseline Characteristics

Patient characteristics	Total (N = 20)	Cohort 1 (n = 10)	Cohort 2 (n = 10)
Mean age, years (range)	66.8 (40-87)	61.7 (40-86)	71.9 (55-87)
Males, n (%)	9 (45)	5 (50)	4 (40)
Mean duration of CRVO symptoms, weeks (range)	17.1 (4-52)	20.7 (6-52)	13.4 (4-26)
Mean baseline VA, ETDRS letters (SEM)	51.6 (3.7)	56.6 (3.0)	46.5 (3.7)
Mean baseline retinal thickness, µm (SEM)	610.5 (47.3)	616.2 (29.0)	604.8 (62.2)

CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; SEM, standard error of the mean; VA, visual acuity.

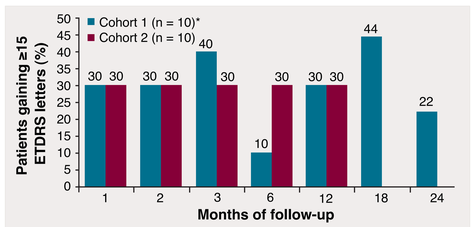
Visual Outcomes

Figure 2. Mean change in BCVA from baseline over time.



*For cohort 1, n = 9 during months 13-24.
BCVA, best-corrected visual acuity (in ETDRS letters). Error bars represent the standard error of the mean.

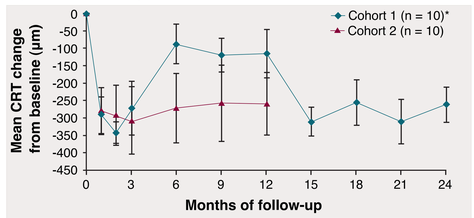
Figure 3. Percentage of patients gaining ≥15 letters of best-corrected visual acuity from baseline over time.



*For cohort 1, n = 9 during months 13-24.

Anatomical Outcomes

Figure 4. Mean change in CRT from baseline over time.



*For cohort 1, n = 9 during months 13-24.
CRT, central retinal thickness. Error bars represent the standard error of the mean.

Table 2. Mean Retinal Vein Diameter

	BL	Month 6	% decrease from BL	Month 12	% decrease from BL	Month 18	% decrease from BL	Month 24	% decrease from BL
Cohort 1	151.9 µm	127.5 µm	16.1	135.7 µm	10.7	130.9 µm	13.9	134.0 µm	11.83
n =	8	8		8		7		8	
Cohort 2	151.9 µm	137.5 µm	9.5	123.0	19.0	-	-	-	
n =	9	9		9		-	-	-	

Case Studies

Case 1: A 70-year-old female patient from cohort 1 who had received 13 ranibizumab (0.5 mg) injections as of month 24 (Figures 5A, 5B).

Figure 5A. Color fundus photograph and OCT images.

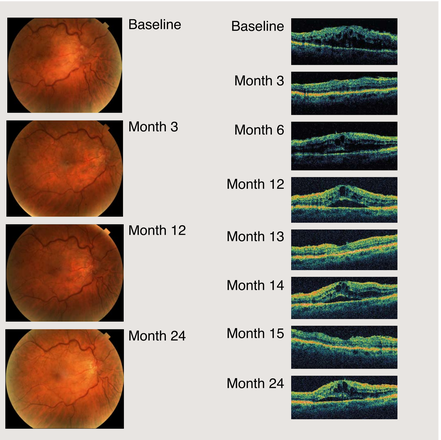
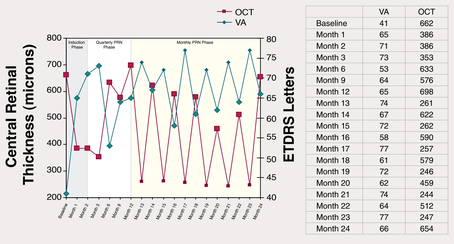


Figure 5B. CRT and VA over time.



	VA	OCT
Baseline	41	662
Month 1	65	386
Month 2	71	386
Month 3	73	353
Month 6	53	633
Month 9	64	576
Month 12	65	698
Month 13	74	261
Month 14	67	622
Month 15	72	262
Month 16	58	590
Month 17	77	257
Month 18	61	579
Month 19	72	246
Month 20	62	459
Month 21	74	244
Month 22	64	512
Month 23	77	247
Month 24	66	654

Case 2: A 61-year-old male patient from cohort 2 who had received 6 ranibizumab (0.3 mg) injections as of month 12 (Figure 6).

Figure 6A. Color fundus photograph and OCT images.

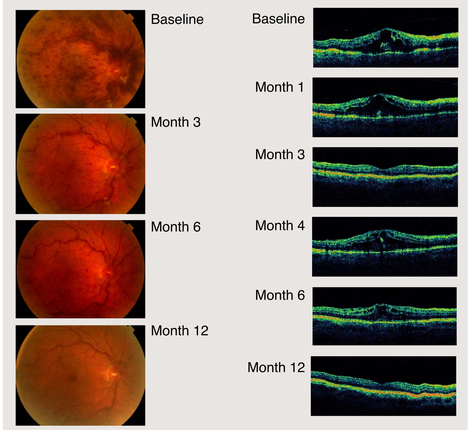
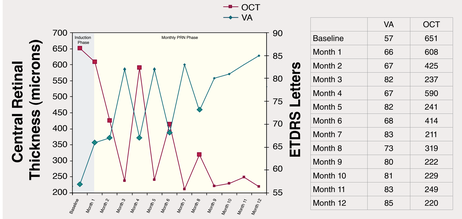


Figure 6B. CRT and VA over time.



	VA	OCT
Baseline	57	651
Month 1	66	608
Month 2	67	425
Month 3	82	237
Month 4	67	590
Month 5	82	241
Month 6	68	414
Month 7	83	211
Month 8	73	319
Month 9	80	222
Month 10	81	229
Month 11	83	249
Month 12	85	220

Safety

- One patient in cohort 1 (0.3 mg) showed a significant decrease in CRT by OCT, with associated improvement in BCVA after initial ranibizumab injections through month 2. During follow-up from month 3 through month 12, the patient developed a severe recurrence of macular edema between treatments at month 3, 6, 9, and 12. The patient experienced a continued decline in vision compared with baseline, with recurrent macular edema, macular ischemia, and increased intraretinal hemorrhage, despite continued ranibizumab treatment. (The patient withdrew after completing year 1 because she moved out of state.)
- One patient in cohort 2 (0.5 mg) with a previous history of coronary artery disease experienced a mild myocardial infarction that was confirmed by coronary angiography. The patient underwent triple bypass surgery without complication and resumed participation in the clinical trial after missing 1 study visit.
- No other severe ocular or nonocular AEs were observed.

CONCLUSIONS

- Improvement in visual outcomes
  - Ranibizumab treatment (0.3 mg or 0.5 mg) resulted in initial gains in BCVA during months 1 to 3 for both cohorts, with slightly greater mean gains for cohort 1 compared with cohort 2.
  - However, mean BCVA gains in both cohorts decreased following the switch from the induction phase (monthly injection at baseline, month 1, and month 2) to quarterly PRN (cohort 1) or monthly PRN (cohort 2) injections through month 12. This decline in BCVA was greater in magnitude in cohort 1 than in cohort 2.
  - Mean BCVA gains in cohort 1 increased back to induction-phase levels with resumption of monthly PRN injections through month 24.
- Improvement in anatomical outcomes
  - Ranibizumab treatment resulted in mean reductions from baseline CRT in both cohort 1 and cohort 2 patients at months 1 to 3.
  - In cohort 1 patients, the initial improvement was lost with the switch to quarterly PRN treatment during months 3 to 12, but was recovered upon resumption of monthly PRN treatment in months 13 to 24.
  - In cohort 2 patients, the initial improvement was sustained until month 12.
  - In cohorts 1 and 2, most patients experienced an improvement in retinal vein diameter over the course of 12 months.
  - Intraretinal hemorrhage was moderate to severe at baseline but improved to none to mild after 12 months.
- Ranibizumab treatment is safe and well tolerated.
- Follow-up is ongoing and will be continued until month 36 for both cohorts.
- These findings merit further investigation and confirmation in larger ongoing and future studies.

REFERENCES

1. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331:1480-1487.
2. Noma H, Funatsu H, Mimura T, Harino S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor in macular edema with central retinal vein occlusion. *Ophthalmology*. 2009;116:87-93.
3. Noma H, Minamoto A, Funatsu H, et al. Intravitreal levels of vascular endothelial growth factor and interleukin-6 are correlated with macular edema in branch retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 2006;244:309-315.
4. Cunningham ET Jr, Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic edema. *Ophthalmology*. 2005;112:1747-1757.
5. Chun DW, Heier JS, Topping TM, et al. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. *Ophthalmology*. 2006;113:1706-1712.
6. Nguyen QD, Tatlipinar S, Shah SM, et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. *Am J Ophthalmol*. 2006;142:961-969.
7. Campochiaro PA, Hafiz G, Shah SM, et al. Ranibizumab for macular edema due to retinal vein occlusions; implication of VEGF as a critical stimulator. *Mol Ther*. 2008;16:791-799.

Commercial relationships: J. Basefsky, N; **D. Pieramici,** Genentech, Novartis, QLT, Surmodics - C; **R. Avery,** Alcon, EyeTech, Genentech, Novartis, QLT, OSI/ Pfizer, Neovista, Regeneron - C; **M. Nasir** - N; **A. Castellarin** - N; **M. Rabena** - N; **S. Risard**, N.

Acknowledgments: This study was funded by Genentech, Inc. Support for third-party writing assistance was provided by Genentech, Inc.

CALIFORNIA RETINA CONSULTANTS AND RESEARCH FOUNDATION

Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Fort Lauderdale, FL; May 3-7, 2009