

TOPIC HIGHLIGHT

Comparison of Anti-VEGF, Steroid, and Combination Therapy in the Treatment of Retinal Vein Occlusion

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ABSTRACT

Macular grid laser photocoagulation was the standard therapy for RVO (retinal vein occlusion) for many years, but several newer studies have come along in the last 6 years that introduced new injectable agents like anti-vascular endothelial growth factor (anti-VEGF) and corticosteroids. The BRAVO, CRUISE, Galileo and Copernicus studies looked at anti-VEGF as treatment, and the Ozurdex/Geneva study and SCORE involved corticosteroids. The Ozurdex/Geneva study compared intravitreally injected dexamethasone implant with a sham in both CRVO and BRVO patients. Patients received either 2 injections of 700- μ g dexamethasone intravitreal implant (Ozurdex, Allergan) 6 months apart or 1 sham injection and then 1 implant injection 6 months later. The data showed that sustained-release dexamethasone (Ozurdex, Allergan) was effective in treating macular edema in BRVO and CRVO, and patients had a mean improvement in BCVA (best corrected visual acuity) of about 10 letters. When patients were reinjected, they achieved the same improvement in visual acuity in the second 6 months. The SCORE study investigated a special preparation of triamcinolone (Trivaris, Allergan). Patients were injected with the agent every 4 months. The results showed that for CRVO, triamcinolone was superior to observation, and for BRVO,

laser was better than triamcinolone. The BRAVO and CRUISE studies observed how well intravitreal injections of ranibizumab worked to treat BRVO and CRVO, respectively. The BRAVO data showed a gain of 18.3 letters in BCVA with a 0.5-mg injection, 16.6 letters with a 0.3-mg injection, and 7.3 letters in the sham group. The CRUISE study showed similar 6-month results, with patients gaining 14.9 letters in the 0.5-mg group, 12.7 letters in the 0.3-mg group, and 0.8 letters in the sham group. The Galileo and Copernicus studies evaluated monthly aflibercept for the treatment of macular edema in patients with CRVO. In both studies, patients received monthly injections for 6 months with the agent or with a sham injection. In Copernicus, all patients were switched to as needed dosing at 6 months, while in Galileo only patients initially treated with the agent were retreated on an as-needed basis. At 1 year, the mean change in vision was + 16.2 letters in the aflibercept group in Copernicus and + 16.9 letters in the Galileo group, versus + 3.8 letters in both sham groups. A recent emerging idea is to treat RVO with both intravitreal sustained-release dexamethasone and anti-VEGF agents (combination therapy) which has been shown to improve visual acuity and prolong the time between injections (reinjection interval). In our study, patients with both CRVO and BRVO received anti-VEGF injections (either bevacizumab, ranibizumab, or aflibercept) followed by 0.7-mg dexamethasone intravitreal implant (Ozurdex) 2 weeks later. Patients were evaluated every 2-4 weeks until the next anti-VEGF injection. The mean BCVA increased from 9.4 to 16.8 letters during the course of the initial study (by 6 months), and the mean peak improvement in BCVA across all re-treatment cycles was 12.5 letters for BRVO and 20.1 letters for CRVO (a longer term evaluation). This study showed that the addition of dexamethasone intravitreal implant 2 weeks following anti-VEGF therapy provides improvements in BCVA and macular thickness in patients with RVO and increases the percentage of patients whose macula was essentially fluid-free compared with anti-VEGF therapy alone.

Key words: RVO (Retinal Vein Occlusion); CRVO (Central Retinal Vein Occlusion); BRVO (Branch Retinal Vein Occlusion); anti-VEGF (anti-vascular endothelial growth factor); Dexamethasone intravitreal implant (Ozurdex)

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INTRODUCTION

Macular grid laser photocoagulation was the standard therapy for RVO (retinal vein occlusion) for many years. In 1984, it was proven to be effective for treatment for BRVO (branch retinal vein occlusion), specifically the associated macular edema, as demonstrated by the Branch Vein Occlusion study^[1]. The study results showed laser therapy improved vision by 1.33 lines, compared with 0.23 lines with just observation. The 1995 Central Vein Occlusion Study showed laser photocoagulation as a treatment for macular edema in CRVO (central retinal vein occlusion) did improve angiographic findings, but was not as effective in improving vision^[2].

Several newer studies have since come along in the last 6 years that introduced new injectable agents like anti-vascular endothelial growth factor (anti-VEGF) and corticosteroids. The BRAVO, CRUISE, Galileo and Copernicus studies looked at anti-VEGF as treatment, and the Ozurdex/Geneva study and SCORE involved corticosteroids.

STEROID STUDIES

The Ozurdex/Geneva study compared intravitreally injected dexamethasone implant with a sham in both CRVO and BRVO patients. This 6-month study was followed by a 6-month open-label follow-up. In the study phase, patients received either 2 injections of a 700- μ g biodegradable dexamethasone intravitreal implant (Ozurdex, Allergan) 6 months apart or 1 sham injection and then 1 implant injection 6 months later. Patients were seen at 1, 2, 3 and 6 month visits. The same visit schedule repeated in the second 6 months. Patients with 20/20 vision or OCT < 225 μ m did not receive a second injection.

The data showed that sustained-release dexamethasone (Ozurdex, Allergan) was effective in treating macular edema in BRVO and CRVO. Patients had a mean improvement in BCVA (best corrected visual acuity) of about 10 letters, which peaked at day 60, and 29.3 percent gained 15 or more letters compared to placebo. When patients were reinjected, they achieved the same improvement in visual acuity in the second 6 months^[3]. In addition, 20% of patients needed only a single injection to achieve 20/20 vision and OCT < 250 μ m, and did not require another injections for the entire course of the 1-year study. In terms of IOP (intraocular pressure), 15% of patients had an elevation > 25 mmHg at day 60, but only 1.2% had such an elevation by day 180^[4].

The SCORE study investigated a special preparation of triamcinolone (Trivaris, Allergan). Patients were injected with the agent every 4 months unless they attained 20/20 vision or OCT < 225 μ m, making further treatment unnecessary, or the treatment was contraindicated due to intraocular pressure (IOP) elevation, or the treatment was determined futile on the basis of OCT imaging or a lack of increase in visual acuity or no decrease in OCT over 8 months.

The results showed that for CRVO, triamcinolone was superior to observation both initially and at 1 and 2 years^[4]. They also showed

that for BRVO, laser was better than triamcinolone at 1,2 and 3 years^[5]. IOP-lowering drugs were required in both CRVO and BRVO studies: in 7% and 3% respectively, of the standard care groups; 18% and 11%, respectively, of the 1-mg groups; and 32% and 57%, respectively, of the 4-mg groups.

ANTI-VEGF STUDIES

The BRAVO and CRUISE studies were 12-month studies that observed how well intravitreal injections of ranibizumab worked to treat BRVO and CRVO, respectively. In both studies, patients received either monthly ranibizumab injections or monthly sham injections for the first 6 months. Then, after month 6, the patients in the sham group in BRAVO received monthly injections as needed and rescue laser. The patients in the sham group in CRUISE had a 6-month observation period with monthly injections as needed after month 6. Patients were seen monthly throughout both studies.

At 6 months, the BRAVO data demonstrated a gain of 18.3 letters in best corrected visual acuity (BCVA) in the 0.5-mg group, 16.6 letters in the 0.3-mg group, and 7.3 letters in the sham group. In addition, approximately 60% of patients in the 0.5-mg group gained 3 lines of vision in contrast to 7.3% in the sham group^[6].

The CRUISE study showed similar 6-month results, with patients gaining 14.9 letters in the 0.5-mg group, 12.7 letters in the 0.3-mg group, and 0.8 letters in the sham group. About 47% of patients in the 0.5-mg and 0.3-mg groups gaining 3 lines of vision versus 16.9% in the sham cohort. In both the BRAVO and CRUISE studies, patients received monthly injections in the first 6 months. The 12-month data showed that these effects were sustained with an average of approximately 3 additional injections^[7].

The Galileo and Copernicus studies evaluated monthly aflibercept for the treatment of macular edema in patients with CRVO. In both studies, patients were injected monthly for 6 months with the agent or with a sham preparation. In Copernicus, all patients were switched to as needed dosing at 6 months, while in Galileo only patients initially treated with the agent were allowed to be retreated on an as-needed basis. Retreatment criteria included: an increase on >50 μ m in central macular thickness from lowest previous measurement, new or persistent cystic retinal changes or subretinal fluid or persistent diffuse edema > 250 μ m in central subfield, loss of > 5 letters from best previous measurement with any increase in central retina thickness, or increase of > 5 letters between current and most recent visit.

At 1 year, the mean change in vision was + 16.2 letters in the aflibercept group in Copernicus and + 16.9 letters in the Galileo group, versus + 3.8 letters in both sham groups^[8,9]. The proportion of patients who gained > 15 letters was 60.2% in the treated group versus 32.4% in the sham group in Galileo, and 55.3% in the treated group versus 30.1% in the sham group in Copernicus^[10].

COMBINATION THERAPY

A more recent emerging idea is to treat RVO with both intravitreal sustained-release dexamethasone and anti-VEGF agents. Treatment with monotherapy of anti-VEGF agents works well, but has its limitations. One example is there are some cases of resistance that begins to develop. This is possibly due to incomplete effect or rebound retinal edema when the injections are switched from monthly to as needed. Also, the duration of effect of a given injection is not known, and neither is the number of injections necessary to control the disease. Another concern is how often patients should

be followed in order to maximize the effect while decreasing the incidence of rebound edema. Combination therapy may alleviate these concerns as it has been shown to improve visual acuity and prolong the time between injections (reinjection interval).

For about 5 years, our practice and others^[11,12,13] have studied the effects of combining anti-VEGF medications with dexamethasone intravitreal implants to determine improvement in visual acuity, CFT (central foveal thickness) and the sustainability of multiple applications of combination therapy in RVO. Our study was a prospective, institutional review board-approved trial in which patients with both central and branch vein occlusions received anti-VEGF injections (either bevacizumab, ranibizumab, or aflibercept) followed by a 0.7-mg dexamethasone intravitreal implant (Ozurdex) 2 weeks later. Inclusion criteria: patients with CRVO or BRVO with visual acuity of 20/40 to 20/200 (Snellen acuity) and OCT > 300 μm (as measured by Cirrus OCT), patients that were anti-VEGF naïve, or had received prior anti-VEGF therapy (> 6 weeks prior), and patients that had received 3 treatment cycles of anti-VEGF and dexamethasone injections or had follow up greater than 14 months^[11]. Exclusion criteria included patients that had a vitrectomy, rubeosis, or advanced glaucoma^[8,9].

The primary outcome was the time to retreatment; secondary outcomes included central foveal thickness (using OCT), visual acuity (Snellen) and safety (cataracts and percentage of patients with IOP > 23 mmHg). All patients were treated with anti-VEGF agents (either bevacizumab, ranibizumab, or aflibercept) at baseline, and all received a dexamethasone intravitreal implant 2 weeks later. Evaluations were carried out at baseline (visit 1), week 2 (visit 2), week 4 to 6 (visit 3), and every 4 weeks thereafter, until the next anti-VEGF injection. Patients were retreated with anti-VEGF agents if retinal thickness increased to > 290 μm, or if the visual acuity had decreased by 6 Snellen letters^[11].

Our initial analysis was initially published in 2012^[11], which looked at patients treated for up to 6 months with bevacizumab or

ranibizumab and DEX implant. A more recent long term analysis was done to determine if there was any change in effectiveness of combination therapy over time as well as to determine any new safety signals^[14]. In the initial analysis, 34 eyes of 33 patients (*n* = 34) participated in the study. The mean BCVA increased from 9.4 to 16.8 letters during the course of the study (Figure 1)^[11]. The mean change in OCT-measured retinal thickness decreased by 154 μm at 2 weeks with an additional 61 μm decrease seen at weeks 4 and 6 (Figure 2)^[11]. In our more recent study, 62 eyes of 60 patients were evaluated (*n* = 62). CRVO was present in 22 patients and BRVO in 40. Fourteen patients had received prior bevacizumab therapy. The age range was 38 to 98 years old, with 68% female and 32% males.

The mean cycle time of all patients was 134 days. Fifty cycles (21%) had a cycle length of 6 months or greater, and of the patients who had cycles of less than 6 months in length, the mean cycle length was 120 days. Additionally, there was no statistically significant difference in mean intertreatment interval among six injection cycles, suggesting that the reinjection interval does not change over time. The mean peak improvement in BCVA across all treatment cycles

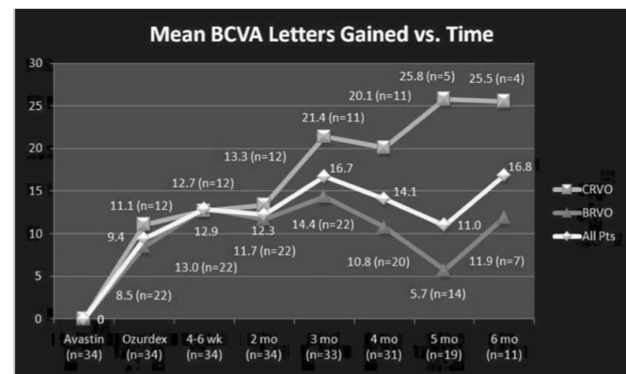


Figure 1 Mean visual acuity improvement over time overall and divided by disease types^[11]. (Reprinted from Retina pg 1291)

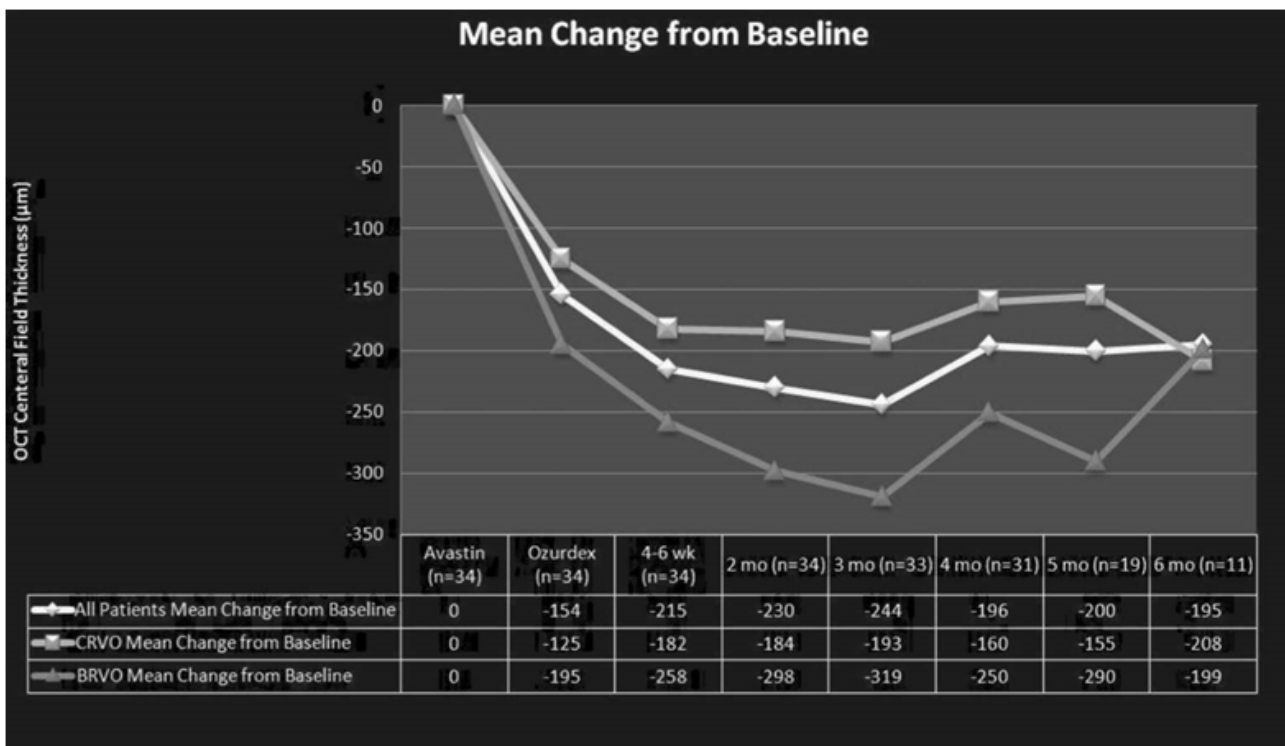


Figure 2 Reduction in central field thickness on spectral-domain OCT over time, overall, and divided by disease type^[11]. (Reprinted from Retina pg 1292).

was 12.5 letters (range 7.4 to 16.3 letters) for eyes with BRVO and 20.1 letters (range 10.4 to 27.9 letters) for eyes with CRVO. Participants who gained at least 3 lines (15 letters or more) of BCVA at any time during a given treatment cycle ranged from 35% to 67% for eyes with BRVO and 43% to 60% for eyes with CRVO. The mean peak decrease in CFT across all treatment cycles was 200.9 μm for eyes with BRVO and 219.2 μm for eyes with CRVO. The percentage of patients with CFT ≤ 300 μm at any time during a given treatment cycle ranged from 78% to 94% among eyes with BRVO and from 85% to 100% among eyes with CRVO.

Forty-four patients were phakic at the beginning of the study, with 26 eyes (59%) having cataract surgery during the study. In terms of IOP increases at any point during the study, 45% had IOP > 23 mmHg, 25% with IOP > 25, 15% with IOP > 30, and 4% with IOP > 35. No patient underwent incisional surgery and only one patient received SLT (selective laser trabeculoplasty). Among eyes that developed increased IOP, the increase occurred within the first or second injection cycle in 75% of cases, and 92% of cases had an increase within the first three cycles.

The combination study showed that the addition of dexamethasone intravitreal implant 2 weeks following anti-VEGF therapy provides improvements in best corrected visual acuity and macular thickness in patients with retinal vein occlusion. Combination therapy also increases the percentage of patients whose macula was essentially fluid-free compared with anti-VEGF therapy alone^[10]. All these affects demonstrate a long-range predictability with cycle lengths of approximately 4 months, as well as being able to detect the timing of possible increases in intraocular pressure. This can provide a long-term benefit for those patients that are burdened by monthly office visits, as it may necessitate fewer than 3 cycles of injections per year.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

- 1 Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmology*. 1984; **98**: 271-282
- 2 Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. *Ophthalmology*. 1995; **102**: 1425-1433
- 3 Haller JA, Bandello F, Belfort R, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon Y, Jacques ML, Jiao J, Li XY, Whitcup SM, OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010; **117**: 1134-1146
- 4 SCORE Study Research Group. *Arch Ophthalmol*. 2009; **127**: 1101-1114. Erratum in: *Arch Ophthalmol*. 2009; **127**: 1655
- 5 SCORE Study Research Group. *Arch Ophthalmol*. 2009; **127**: 1115-1128. Erratum in: *Arch Ophthalmol*. 2009; **127**: 1655
- 6 Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC, Murahashi WY, Rubio RG, BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six month primary end point results of a phase III study. *Ophthalmology*. 2010; **117**: 1102-1112
- 7 Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, Rundle AC, Rubio RG, Murahashi WY, CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six month primary end point results of a phase III study. *Ophthalmology*. 2010; **117**: 1124-1133
- 8 Boyer D, Heier J, Brown DM, Clark WL, Vitti R, Berliner AJ, Groetzbach G, Zeitz O, Sandbrink R, Zhu X, Beckmann K, Haller JA. Vascular Endothelial Growth Factor Trap-Eye for Macular Edema Secondary to Central Retinal Vein Occlusion: Six-Month Results of the Phase 3 COPERNICUS Study. *Ophthalmology*. 2012; **119**: 1024-1032
- 9 Brown DM, Heier JS, Clark WL, Boyer DS, Vitti R, Berliner AJ, Zeitz O, Sandbrink R, Zhu X, Haller JA. Intravitreal aflibercept injection in central retinal vein occlusion: 1-year results of the phase III COPERNICUS Study. Poster presentation at Association for Research in Vision and Ophthalmology (ARVO) 2012 annual meeting. May 6-10, 2012. Fort Lauderdale, FL.
- 10 Ogura Y (Japan) for the GALILEO study Investigators. Vascular endothelial growth factor trap-eye for macular edema in central vein occlusion – 52 week results of phase III Galileo study. Presented at World Ophthalmology Congress 2012, Abu Dhabi, United Arab Emirates.
- 11 Singer MA, Bell DJ, Woods P, Pollard J, Boord T, Herro A, Porbandarwalla S. Effect of Combination Therapy with Bevacizumab and Dexamethasone Intravitreal Implant in Patients with Retinal Vein Occlusion. *Retina* 2012; **32**(7): 1289-1294.
- 12 Singer MA, Capone A Jr, Dugel PU, Dreyer RF, Dodwell DG, Roth DB, Shi R, Walt JG, Scott LC, Hollander DA; SHASTA Study Group. Two or more dexamethasone intravitreal implants as monotherapy or in combination therapy for macular edema in retinal vein occlusion: subgroup analysis of a retrospective chart review study. *BMC Ophthalmol*. 2015 Apr 1; **15**: 33.
- 13 Bakri SJ, Omar AF, Iezzi R, Kapoor KG. Evaluation of Multiple Dexamethasone Intravitreal Implants with Macular Edema Associated with Retinal Vein Occlusion, Macula Society Meeting 2014, Key Largo, Florida.
- 14 Singer, MA, Tyler, LT, Woods P, Singer JS, Bell, DB. Long term Analysis of Combination Therapy using Anti- Vasoendothelial Growth Factor Medications and Dexamethasone Intravitreal Implant Injection for retinal Vein Occlusion presented at the 2014 Club Jules Gonin meeting in Zurich Switzerland and Retina Society Philadelphia, PA in September 2014

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