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Title:

Short-term safety of dexamethasone implant for treatment of macular edema due to retinal vein occlusion, in eyes with glaucoma or treated ocular hypertension

Authors:

Sofia Theodoropoulou,[1] Abdallah A Ellabban,[2] Robert L Johnston,[2] Helena Cilliers,[3] Quresh Mohamed,[2] Ahmed B Sallam[2,4]

1. School of Clinical Sciences, University of Bristol and Bristol Eye Hospital, Bristol, United Kingdom.
2. Gloucestershire Eye Unit, Cheltenham General Hospital, Sandford Road, Cheltenham, United Kingdom.
3. Ophthalmology Department, South Warwickshire NHS Foundation Trust, Warwick, United Kingdom.
4. Jones Eye Institute, University of Arkansas for Medical Sciences, Arkansas, United States.

Corresponding Author:

Ahmed Sallam MD, PhD, FRCOphth

Jones Eye Institute

University of Arkansas for Medical Sciences

Little Rock, Arkansas, 72205

United States

Office: +1-501-526-6000 x 1225

Fax: +1-501-603-1289

Email: ahmedsallam11@yahoo.com

Abstract

Purpose: To report the short-term safety of dexamethasone implants to treat macular edema due to retinal vein occlusion (RVO), in eyes with treated glaucoma or ocular hypertension at baseline using an as-needed re-treatment regimen.

Methods: Retrospective clinical database study from 2 centers using the same electronic medical record system. Extracted data included: intraocular pressure (IOP), visual acuity (VA), central 1mm retinal thickness (CRT) by optical coherence tomography, phakic status, number of injections, glaucoma treatment, and peri-operative complications.

Results: Thirty-three eyes of 33 patients on IOP-lowering treatment for glaucoma or ocular hypertension (OHT) at baseline and mean IOP of 16mmHg at baseline received 1 to 4 (mean, 1.8; median, 1) dexamethasone implants over 18 months for RVO-related macular edema. Fourteen eyes (42%) had IOP of ≥21 mmHg, and three eyes (9%) had IOP of ≥35 mmHg at 1 or more visits during the study period. Nine of 14 eyes (64%) with raised IOP required additional topical treatment only for a mean (SE) period of 8.5 months (3.2), while the remaining 5 eyes (36%) required long-term additional IOP-lowering treatment for a mean (SE) of 16 months (1.44). Surgery for IOP lowering was not required in any eye. Mean VA (SE) improved from 44 (3) ETDRS letters at baseline to 47 letters (5) at 2 months ($p=0.049$), 48 (8) letters at 6 months and 46 (4) letters at 12 months. Mean CRT (SE) improved from 530 (25) µm at baseline to 323 (27) µm at 2 months ($p<0.001$), 498 (76) µm at 6 months and 359 (25) µm at 12 months ($p<0.001$).

Conclusion: The short-term IOP rise after intravitreal dexamethasone implant in eyes with glaucoma or ocular hypertension at baseline was acceptable and consistent with previous reports in patients without preexisting glaucoma. Treated OHT or glaucoma may not be a strict contraindication against the use of dexamethasone implant but close monitoring of IOP is required.

Key words:

Dexamethasone implant; glaucoma; macular edema; ocular hypertension; retinal vein occlusion

Introduction

Retinal vein occlusion (RVO) is the second most common cause of vision loss due to retinal vascular disease, after diabetic retinopathy [1,2]. Until 2011, the standard of care for the treatment of macular edema from RVO was defined by the findings of the Branch Retinal Vein Occlusion Study and Central Retinal Vein Occlusion Study, that recommended grid laser photocoagulation for macular edema in non-ischemic branch RVO (BRVO) and observation of macular edema in central RVO (CRVO) [3-5]. Options for treatment of macular edema associated with RVO have, however, expanded in the past few years with the introduction of intravitreal corticosteroid treatments [6-8] and intravitreal treatment targeted against vascular endothelial growth factor (VEGF) [9-15].

In the United Kingdom (UK), the sustained-release dexamethasone implant (Ozurdex, Allergan, Irvine, California, USA) was the first intravitreal treatment approved by National Institute for Health and Care Excellence (NICE) for treatment of macular edema due to RVO in July 2011, leading to its widespread adoption by the National Health Service (NHS). Ranibizumab treatment was approved by NICE for the same indications in May 2013 and aflibercept was approved for macular edema due to CRVO in February 2015 and for BRVO in September 2016. Accordingly, during the period of July 2011 to May 2013, dexamethasone implant was used nearly exclusively for treatment of RVO, apart from a few cases treated by bevacizumab as an off-license treatment [7].

Dexamethasone implant treatment for macular edema in RVO has been shown in clinical trials to be effective for treating RVO with an effect lasting up to 4 months after a single implantation [7,8,16]. Ease of insertion, an acceptable safety profile and prolonged duration of action support its use. The major safety concern has been its impact on IOP. Randomized controlled studies have shown that when intraocular pressure (IOP) rise occurs after dexamethasone implant injections is usually short-lived, moderate in severity, and readily managed with IOP-lowering therapy [7,8]. Nevertheless, patients using IOP-lowering medications were excluded from the phase 3 studies of dexamethasone implant treatment in RVO [7,8]. In a 'real–world' clinical setting, approximately one third of the patients with RVO may have pre-existing glaucoma or OHT, and be using IOP-lowering medication [17]. This is not unexpected because these conditions are known risk factors for RVO [18].

The purpose of this study was to audit 'real-world' data on the use of dexamethasone implants in patients with RVO and pre-existing glaucoma or OHT already on IOP-lowering treatment, a sub-group that has not been previously analyzed in any studies.

Methods

Study population

We retrospectively reviewed the electronic medical records (EMR) of 33 consecutive eyes (33 patients), who received one or more dexamethasone intravitreal implants for the treatment of macular edema due to RVO from 2 UK eye departments: Gloucestershire Hospitals NHS Foundation Trust and South Warwickshire NHS Foundation Trust, during the period from 1 February 2012 to 30 September 2013. Collection of data was in the context of entirely electronic clinical data entry within an electronic medical record system (Medisoft Ophthalmology, Medisoft Ltd, Leeds, UK). All patients had been diagnosed with primary open angle glaucoma, confirmed with gonioscopy, or OHT and were using IOP-lowering treatment before initiating dexamethasone implant treatment and had at least 18 months of follow-up. For this study, patients were excluded if they were not on IOP-lowering treatment before the first dexamethasone implant, even if they were diagnosed with untreated OHT or were glaucoma suspects. Patients were also excluded if they had less than 18 months of follow-up following their first injection.

All patient identifiers were removed to make data anonymous and the study was conducted in accordance with the declaration of Helsinki and the UK's Data Protection Act of 1998. Anonymized database analyses of this type do not require ethical permission as they are viewed as audit for service evaluation [National Patient Safety Agency (UK). Defining research 2010. http://www.npsa.nhs.uk/nrls/research-and-evidence].

Clinical data

Clinical and demographic data extracted from the EMR included: patients' age at baseline, gender, type of RVO, laterality, previous ocular treatments, all known ocular and systemic co-morbidities, surgical details, number of injections, complications, visual acuity (VA), intraocular pressure (IOP), central retinal thickness (CRT) assessed by optical coherence tomography (OCT) at baseline, 2 weeks then 4, 6, 8, 12 and 18 months months post-injection of the first intravitreal dexamethasone implant. Fluorescein angiography was performed at baseline only when there was uncertainty about the presence and severity of macular ischemia.

Data sources/measurements

As data were gathered from routine clinical settings, visual acuity was determined as the best VA with habitual VA correction or pinhole rather than best-corrected refracted VA at all time points. If more than one assessment of VA was made during that period, the VA demonstrating the greatest

improvement from baseline (peak effect) was used in the analysis. In patients where data were not available for a particular visit or had been lost to follow-up, no missing value substitutions were performed. Baseline central 1 mm subfield retinal thickness was defined as the last values measured on or before the day of the first dexamethasone implant injection.

Statistical methods

All data are expressed as the mean ± standard error (SE) of the mean. Paired student's test was used to compare patient characteristics and OCT measurements between time points. The incidence rate of complications (IOP rise) and time-to-event analysis was performed using the Kaplan-Meier method. Spearman's correlation test was used to investigate the correlation of the clinical characteristics. All statistical analyses were conducted using the SPSS statistical package (Statistical Package for Social Sciences version 21.0; SPSS, Inc., Chicago, IL). A P-value less than 0.05 was accepted as statistically significant.

Results

Thirty-three eyes of 33 patients who had been diagnosed with glaucoma or OHT and were on IOP-lowering treatment before first dexamethasone implant were included, 22 (67%) with CRVO and 11 (33%) with BRVO. The baseline characteristics of the study population are listed in Table 1. Overall, the mean age of the patients was 81.7 years. The macular edema associated with RVO diagnosis had a mean duration of 14.4 months (range: 0-55 months) at baseline. The mean time between diagnosis of RVO-related macular edema and the first dexamethasone implant treatment was 13.5 months in BRVO patients and 15.4 months in CRVO patients. This long duration of macular edema prior to treatment can be explained by the fact that our study included eyes that were diagnosed since 2009, prior to the approval of any pharmacological treatment (including dexamethasone implant) for RVO in the UK. Fluorescein angiography was performed in eight eyes (24%) at baseline. Five eyes (3 with CRVO and 2 with BRVO), which were included in the study (15%), had ischemia confirmed with fluorescein angiography. The majority of the eyes included in our study, 27 eyes (82%) had been diagnosed with glaucoma with the rest 6 eyes (18%) being diagnosed with OHT, all receiving IOP lowering substances. IOP was controlled with one topical substance in 17 eyes (51.5%), with the rest being on two topical substances and one eye being on triple therapy (Table 1). None of the study eyes had previous glaucoma surgery or received oral acetazolamide treatment at baseline.

Other than for glaucoma and OHT, most of the eyes (76%) were treatment-naive and had not received intravitreal or laser treatment for RVO-associated complications before the first

dexamethasone implant. The remaining eyes, had other treatment before beginning dexamethasone implant treatment, where 5 eyes (15%) had intravitreal anti-VEGF treatment, 2 eyes (6%) had focal and/or panretinal laser photocoagulation in addition to anti-VEGF treatment, and one eye (3%) received sequential treatment with intravitreal triamcinolone treatment, intravitreal anti-VEGF treatment and and underwent pars plana vitrectomy surgery. None of the patients had a history of steroid-induced ocular hypertension. The period for data collection from the time of the first dexamethasone implant injection was at least 18 months to up to 24 months. The number of dexamethasone implants received over the follow period ranged from 1 to 4 (mean, 1.8; median, 1) and was similar for both BRVO and CRVO: 1.8 (0.1) in BRVO, and 1.8 (0.1) in CRVO \ Of 33 study eyes, 11 (33%) were switched to anti-VEGF treatment after the first dexamethasone implant. Reasons for using anti-VEGF were: development of rubeosis / neovascular glaucoma in 4 eyes, no anatomical response of macular edema in 5 eyes, and significant increase in IOP (>35mmHg) in 2 eyes (6% of study population).

Among all eyes, 14 eyes (42%) had an IOP of 21 mmHg or higher at any time during the follow up period, while all eyes had IOP less than 21mmHg at baseline (mean, 16mmHg). A rise in IOP to 25mmHg or more was seen in 11 eyes (33%) following their first dexamethasone implant, and 3 eyes (9%) (3 eyes) had IOP of 35 mmHg or higher at 1 or more visits during the study period. Figure 1 demonstrates the timing of IOP rise. The rise in IOP was observed in the period from 2 weeks to 2 months after first dexamethasone implant injection (p-value=0.006 and 0.001, at 2 weeks and 2 months respectively). There was no correlation of IOP rise with the number of IOP-lowering substances at baseline before first injection (Spearman's correlation co-efficient rho=0.286; p-value=0.107). In eyes that received repeat intravitreal implants (16/33 eyes; 48.5 %), comparing the incidence of IOP rise after the first and subsequent treatments did not show a significant difference (figure 2).

Raised IOP was medically treated in all the cases and none of our patients needed incisional surgery. Nine of 14 eyes (64.2%) with raised IOP were treated with topical therapy only, but 5 out of 14 (35.8% of eyes) required the addition of oral acetazolamide. Nine of 14 patients with raised IOP needed the additional topical treatment only while dexamethasone implant remained in vitreous for an average period (SE) of 8.5 months (3.2), and 5 of 14 (15% of eyes) required a more long-term change in their IOP-lowering therapy over the entire mean follow up period (SE) of 15.75 months (1.44) (figure 3). All eyes that had an IOP rise underwent gonioscopy to identify other factors that could cause the IOP elevation. Dexamethasone implant was the only factor explaining the IOP elevation, but four eyes with CRVO (12% of total study eyes) went on to develop neovascular glaucoma. These eyes with neovascular glaucoma were treated with a combination of

anti-hypertensive ocular agents, intravitreal bevacizumab injections and panretinal argon laser photocoagulation.

Mean VA (SE) changed from 44 (3) ETDRS letters at baseline to 55 (4) ETDRS letters at week 2, to 47 (5) ETDRS letters at 2 months, to 45 (4) ETDRS letters at 4 months and to 48 (8) ETDRS letters at 6 months. Mean VA (SE) was 46 (4) and 42 (5) ETDRS letters at 12 and 18 months respectively (figure 4). While there was significant improvement in VA up to 2 months after first dexamethasone injection ($p= 0.049$), mean overall VA improvement at months 4, 6, 12 and 18 from baseline did not show significance ($p= 0.459$, 0.660, 0.776 and 0.726). Mean CRT (SE) improved from 530 (25) µm at baseline to 283 (10) µm at week 2 ($p<0.001$), to 323 (27) µm at 2 months ($p<0.001$) and to 445 (32) µm at 4 months ($p=0.05$). Mean CRT (SE) was 498 (76) µm at 6 months ($p=0.601$), 359 (25) µm at 12 months ($p<0.001$) and 397 (34) µm at 18 months ($p=0.003$) (figure 5). CRT reduction was significant in the first four months after first dexamethasone injection, and remained statistically significant 12 and 18 months after the injection. Eyes with CRVO demonstrated increased CRT reduction compared to those with BRVO (figure 5), however, this difference was not found to be statistically significant at any time point (week 2, and month 2, 4, 6, 12 and 18) after dexamethasone injection.

Regarding other complications from dexamethasone implant, seven patients (7 out of 33 eyes; 21%) underwent cataract surgery during the study period. No case of endophthalmitis, vitreous hemorrhage or retinal detachment was encountered.

Discussion

This study looked primarily at the short-term safety of dexamethasone implants when treating macular edema secondary to RVO, in eyes that had pre-existing glaucoma or ocular hypertension and were on IOP-lowering treatment at baseline. Our results demonstrate that the use of dexamethasone implant in this cohort of eyes is associated with an acceptable safety profile, specifically in relation to the frequency and magnitude of IOP rise. We observed an increase of IOP to >25mmHg in 33% of eyes and 42% of our study eyes required additional topical and/oral treatment for raised IOP, but none required surgery. Repeat dexamethasone implants were not associated with an increased risk of IOP rise compared to the first implant.

The improvement of vision observed after treatment with dexamethasone implant in this study was inferior to that reported in the Phase 3, GENEVA studies of dexamethasone implant for macular edema after RVO [7,8]. In the Phase 3 studies, the cumulative response rate in achieving at least 3-line improvement in VA during the 6 months after the initial treatment with dexamethasone implant was 41% [7], while only 33% of our study eyes had a 3-line improvement in VA at week 4, with this effect wearing off and only 10% of our study eyes having a 3-line improvement in VA

three months after first injection. We would speculate that this could be due to our inclusion of eyes with poor vision at baseline and long duration of vein occlusion before starting treatment. Our re-injection rate was also small with a mean number of approximately 2 implants over 18 months.

The results observed in the current study regarding the IOP rise in patients with pre-existing ocular hypertension or glaucoma is not different to data from randomized pivotal studies [7,8,19,20], although these studies excluded eyes with pre-existing glaucoma or raised IOP. The MEAD study, a randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema, provides the longest safety data on eyes treated with repeat implants with a follow up of 3 years and a mean number of 4.1 implants. Approximately one-third of eyes in the dexamethasone implant treatment groups in the MEAD study, had a clinically significant increase in IOP requiring treatment, no eye underwent removal of the implant to control IOP, and only 1 eye (0.3%) in each treatment group underwent glaucoma incisional surgery for steroid-induced increases in IOP [19]. Similarly, 33% of our study eyes had a rise in IOP, and raised IOP was medically treated in all eyes.

Regarding the effect of multiple treatments on IOP, we observed a rise in IOP in the period from 2 weeks to 2 months after the first dexamethasone implant injection, and in most eyes who had increased IOP, this happened after the second injection. This appears to be similar to eyes without glaucoma as demonstrated in MEAD study where mean IOP peaked at a similar level and returned to baseline levels by 6 months after each dexamethasone implant injection and neither the incidence of IOP adverse events nor the proportion of patients using IOP-lowering treatment increased after subsequent treatments in year 2 or 3 [19]. However, it is of note that only about half of our eyes (48.5%) received more than 1 injection.

To our knowledge this the first study to analyse the safety and efficacy of dexamethasone implants in RVO in eyes with raised IOP on treatment before treatment of macular edema. Two other clinical database studies have included eyes with raised IOP at baseline but neither provided any details on IOP changes or visual acuity outcomes in these subgroups [17,21]. In one of these studies, almost one third of eyes (31.5%) had preexisting glaucoma or ocular hypertension, and 24.2% were using IOP-lowering treatment before receiving their first dexamethasone implant treatment [17]. However, despite the inclusion of eyes with previous IOP rise or glaucoma, the rate of increases in IOP in their overall study population study was comparable to the MEAD Study with 32.8% of eyes treated with 2 dexamethasone implants having at least a 10-mmHg increase in IOP over 1-year and IOP-lowering treatment being required in 29.1% of patients. The ZERO study on reliability and safety of intravitreal dexamethasone implant injections from Germany was the second study to include patients with glaucoma at baseline treated by dexamethasone implant [21]. This study mentioned that in cases with known baseline glaucoma, intraocular pressure elevation

was not more frequent compared to non-glaucoma patients [21], however, the authors did not report any separate sub-group analysis of their glaucoma patients.

Our study has limitations, which include the retrospective design, the lack of randomization and the relatively short follow-up period. Also, we based the outcome of this study on IOP control but did not analyze the impact of elevated IOP in our eyes. While monitoring of intraocular pressure in patients with pre-existing ocular hypertension or glaucoma is crucial, it is possible that the impairment of IOP control in this cohort may result in additional anatomical or functional damage that this study may not captured. Nevertheless, interpretation of functional (visual field testing) or morphological (retinal nerve fiber layer or optic nerve head analysis) tests in the context of RVO is challenging. Finally, it is worth noting that the mean number of re-treatment with dexamethasone implants in our study is small compared to other studies [22,23]. It is therefore possible that our cohort was undertreated and this itself may introduce bias to the results as further IOP rises in eyes with raised IOP or glaucoma may have been mitigated by administering fewer dexamethasone implants.

In summary, the results of this study suggest that the clinical use of dexamethasone implants, has an acceptable safety profile regarding elevated IOP in patients with pre-existing glaucoma or OHT and that the rise in IOP in these eyes could be controlled with additional medical treatment. Our results suggest that similar to eyes that do not exhibit OHT or glaucoma, intravitreal dexamethasone deserves consideration in eyes with controlled OHT or glaucoma when anti-VEGF medications are contraindicated or not effective, but close monitoring is required.

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Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent was not required.

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Figure Legends

Figure 1. Intraocular pressure changes after first injection of intravitreal dexamethasone for retinal vein occlusion. * p-value ≤ 0.001.

Figure 2. Survival curve of time to IOP rise to >25mmHg after first injection of intravitreal dexamethasone for retinal vein occlusion related macular edema. In eyes that received repeat intravitreal implants, IOP rise is observed after the first injection, with no significant difference in incidence following subsequent treatments.

Figure 3. Distribution of additional IOP lowering treatment administered to the patients during the study.

Figure 4. Visual Acuity after first injection of intravitreal dexamethasone for retinal vein occlusion. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion. * p-value ≤ 0.05.

Figure 5. Central retinal thickness after first injection of intravitreal dexamethasone for retinal vein occlusion. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion. * p-value ≤ 0.05, ** p-value ≤ 0.001.

Figure 1

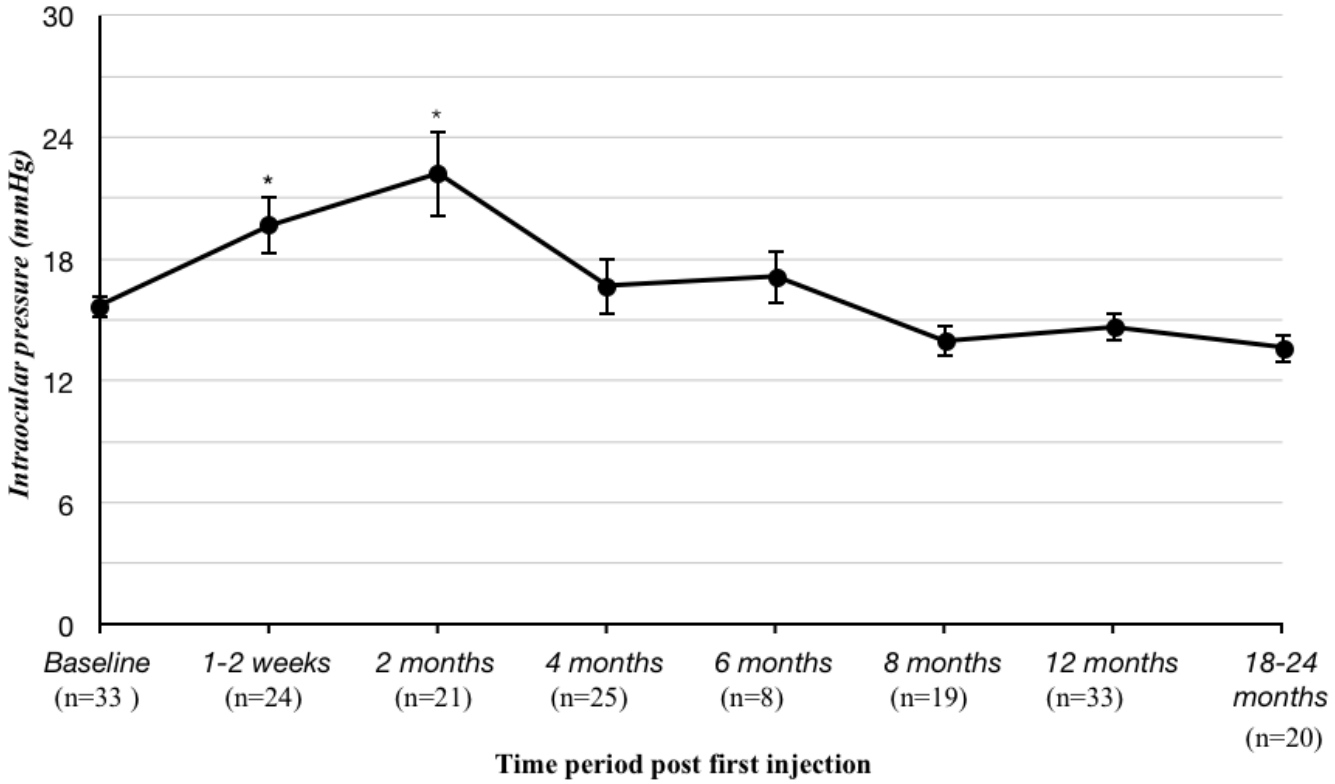

30
24
18
12
6
0
Intraocular pressure (mmHg)
*
*
Baseline (n=33)
1-2 weeks (n=24)
2 months (n=21)
4 months (n=25)
6 months (n=8)
8 months (n=19)
12 months (n=33)
18-24 months (n=20)
Time period post first injection

Figure 4

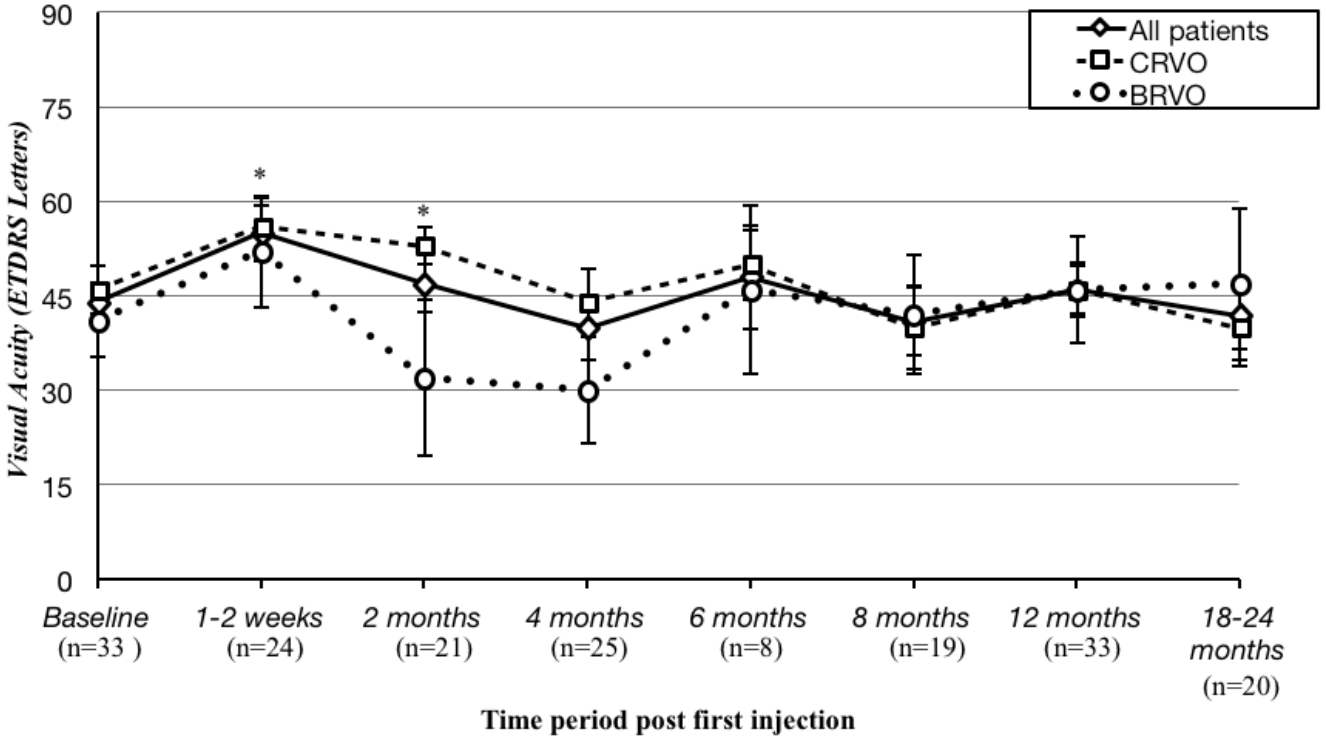
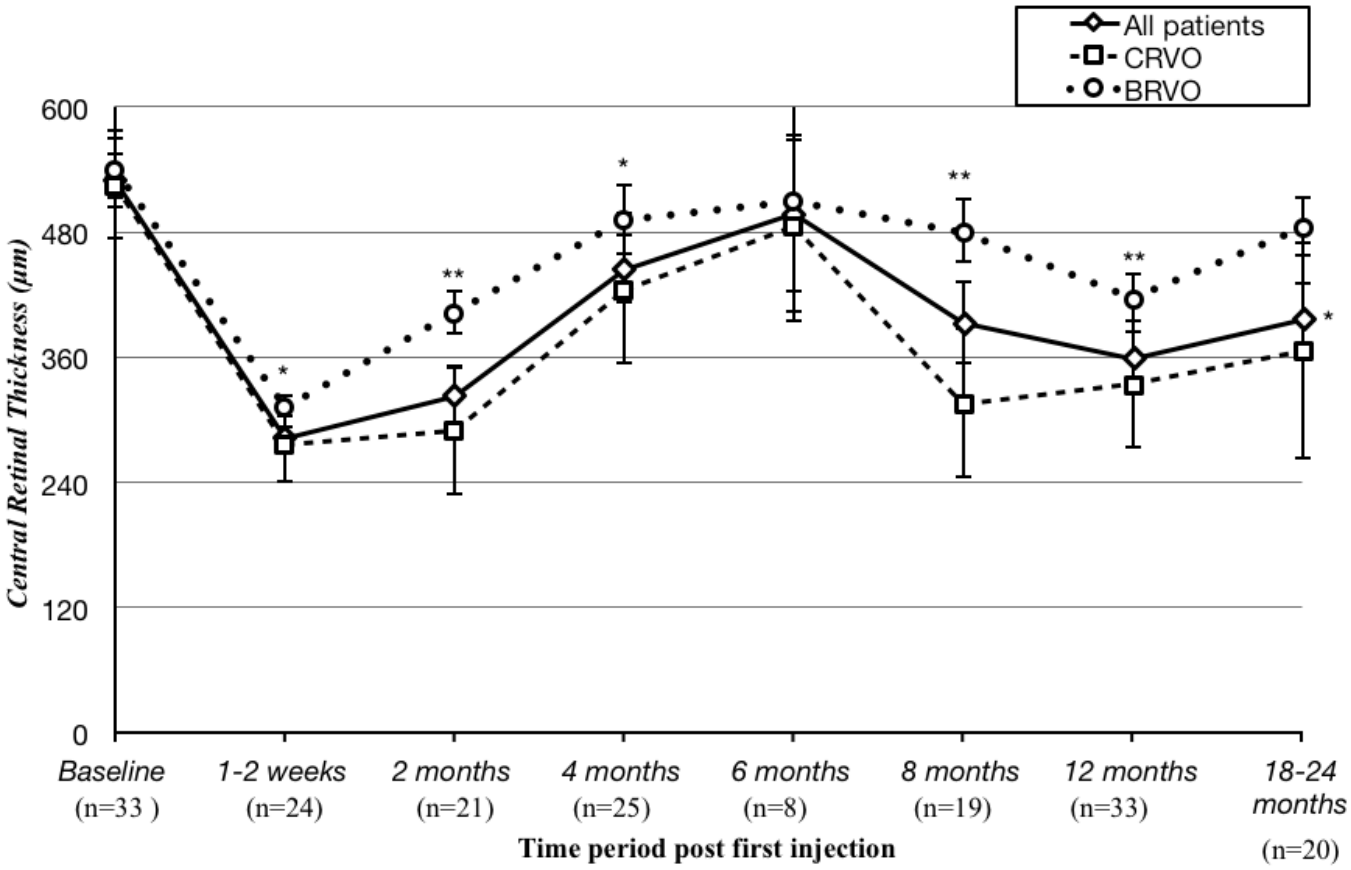

All patients
CRVO
BRVO
Visual Acuity (ETDRS Letters)
90
75
60
45
30
15
0
*
*
Baseline (n=33)
1-2 weeks (n=24)
2 months (n=21)
4 months (n=25)
6 months (n=8)
8 months (n=19)
12 months (n=33)
18-24 months (n=20)
Time period post first injection

Figure 5


All patients
CRVO
BRVO
600
480
360
240
120
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Central Retinal Thickness (µm)
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Baseline (n=33)
1-2 weeks (n=24)
2 months (n=21)
4 months (n=25)
6 months (n=8)
8 months (n=19)
12 months (n=33)
18-24 months (n=20)
Time period post first injection

Table 1. Baseline characteristics of study population

Baseline clinical characteristics of the study population	
Number of eyes (patients)	33 (33)
Type of RVO (n) CRVO BRVO	 22 11
Age, years (mean, SE)	81.7 (1.0)
Baseline VA, ETDRS letters (mean, SE)	44 (3)
Baseline IOP, mmHg (mean, SE)	15 (0.52)
Baseline CMT, μm (mean, SE)	530 (25.47)
Duration of ME prior to treatment, months (mean, SE)	14.38 (3.9)
Number of eyes with ocular comorbidities	
Primary open angle glaucoma	27
Ocular Hypertension (all on medication)	6
Number of lowering IOP substances	
one substance	17
two substances	15
three substances	1