Neovascular glaucoma in patients with central retinal vein occlusion: A real-life study in the anti-VEGF era

Manuel Casselholm de Salles, Charlotte Lindberg and David Epstein

Karolinska Institutet, St. Erik Eye Hospital, Stockholm, Sweden

ABSTRACT.

Purpose: To investigate the characteristics and treatment patterns of patients developing a neovascular event (NE) in the anterior chamber secondary to central retinal vein occlusion (CRVO) in an ordinary clinical setting.

Methods: In this retrospective real-life study, data from 243 eyes presenting with CRVO during 2012–2013 were collected. Maximum follow-up was 5 years. All patients that developed NE were included in the analysis.

Results: Of 243 eligible patients, 72 (30%) either presented with or developed NE during the follow-up. In these 72 patients, 23 (32%) eyes already had evidence of NE at baseline. Twenty-eight eyes (39%) developed NE after discontinuation of intravitreal therapy for macular oedema (ME). In this subgroup, the NE occurred 15.6 ± 13.8 months after the baseline visit and 4.1 ± 2.6 months after the last injection. Final best-corrected visual acuity was 8.6 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the group of patients presenting with NE compared to 8.1 ETDRS letters in the group that developed NE later on. Of the patients presenting with intraocular pressure (IOP) below 30 mmHg, 3/29 (10%) needed subsequent cyclodiode laser therapy compared to 35/43 (81%) patients with a baseline IOP above 30 mmHg (p < 0.001).

Conclusions: In a clinical setting, many patients show evidence of NE already at the first visit. A substantial part of patients develops NE a long time after presentation, commonly a few months after discontinuation of intravitreal therapy for ME. The visual prognosis is similar for patients presenting with NE and patients developing NE during follow-up. A high baseline IOP predicts the need for subsequent pressure-lowering procedures.

Key words: anti-VEGF – central retinal vein occlusion – neovascular glaucoma – real life

Introduction

Central retinal vein occlusion (CRVO) is a common vascular retinopathy that may cause substantial visual loss. Ocular neovascularization is the most feared complication. It most commonly occurs in the anterior part of the eye causing neovascularization of the iris (NVI) and neovascularization of the angle (NVA), the latter often causing neovascular glaucoma (NVG), with elevated intraocular pressure and glaucomatous damage to the optic nerve. A neovascular event (NE) of the anterior chamber typically occurs within 1–4 months after presentation (Hayreh, 1983). Several studies have shown that intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are effective in treating iris neovascularization and serve an important adjuvant treatment modality in patients with NVG (Iliev et al., 2006; Wakabayashi et al., 2008). Early studies showed a low incidence of NVG in patients treated actively with anti-VEGF injections for macular oedema in CRVO (Campochiaro et al., 2011; Epstein et al., 2012; Brown et al., 2013). With the continuous administration of anti-VEGF injections, the risk for developing NVG is low. More recent evidence suggests that anti-VEGF therapy despite having a significant clinical benefit may merely delay the occurrence of NVG in patients with CRVO (Brown et al., 2014; Ryu et al., 2014). However, sparse data exist regarding the time-course of the neovascular process in relation to the last given intravitreal injection. One study showed that NE occurred on average 6 months after the last intravitreal injection in patients treated with bevacizumab and ranibizumab in a pro re nata (PRN) regimen (DeCroos et al., 2014). In our clinic, we use either anti-VEGF injections or sustained-release dexamethasone (Ozurdex®; Allergan Inc., Irvine, CA, USA) as first-line therapy in CRVO patients. Conflicting evidence exists regarding the expression
of intraocular VEGF levels in patients treated with corticosteroids (Sohn et al., 2014; Rezar-Dreindl et al., 2017). In a recent study, no changes in the aqueous VEGF concentrations were observed in patients treated with Ozurdex (Rezar-Dreindl et al., 2017). Hypothetically, patients previously receiving Ozurdex therapy may have a shorter interval between last injection and the onset of NE due to the insignificant anti-VEGF property of dexamethasone. This treatment-free interval is important to determine since anti-VEGF therapy is usually not given indefinitely due to the resolution of the macular oedema, low vision or lack of response to treatment. Some studies have shown that anti-VEGF injections can have an initial pressure-lowering effect in patients with established NVG (Wolf et al., 2011; Sasamoto et al., 2012). How these injections affect the long-time prognosis and the need for subsequent pressure-lowering interventions is unclear. The purpose of this study is to investigate the characteristics of patients developing NE secondary to CRVO in a real-life setting. Additionally, we aim to determine the treatment-free interval until the occurrence of NE in patients treated with Ozurdex as opposed to anti-VEGF injections and to determine the treatment patterns of the increased intraocular pressure and the need for subsequent surgical intervention.

Material and methods

Study population

This retrospective study was performed at St. Erik Eye Hospital, Stockholm, Sweden. Using the hospital’s database, all patients presenting from January 2012 until December 2013 with ICD-10 code H34.8a (CRVO) were retrieved. Using the hospital’s database, this retrospective study was performed at St. Erik Eye Hospital, Stockholm, Sweden. The study adhered to the tenets of the Declaration of Helsinki and the protocol was approved by the regional ethical review board in Stockholm.

Study protocol

A retrospective chart review was performed. Data collected included patient demographics (age, sex), concomitant diseases (glaucoma/ocular hypertension, arterial hypertension, diabetes), best-corrected visual acuity (BCVA), central retinal thickness (CRT), treatment exposure (intravitreal injections, panretinal photocoagulation (PRP), cyclodiode laser therapy, retinal cryoexy) and type of neovascular event (NVG, NVI, NVA). In our clinic, BCVA testing is performed using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol at 4 m (or at 1 m if needed). Optical coherence tomography (OCT) images are captured using Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA). In our clinic, standard treatment for CRVO with ME is anti-VEGF or sustained-released dexamethasone. Drug choice is at the treating doctor’s discretion. If the ME does not respond to one drug, switched therapy may be considered. Intravitreal injections are discontinued if there is no sign of disease, in cases of inactive disease, that is no ME, or if visual acuity is low and does not improve with treatment.

For patients developing NE, PRP is the gold standard treatment in our clinic. Anti-VEGF injections can be given as adjuvant treatment even in the absence of ME. Retinal cryoexy for retinal ischaemia and cyclodiode laser for a painful eye with elevated IOP are considered when the response of PRP is insufficient or as a primary treatment in patients were PRP is not possible. Additionally, intravitreal injections with an anti-VEGF agent or sustained-released dexamethasone are given if a concomitant ME is present. Patients with ME and low visual function that have received definitive treatment, that is PRP, cyclodiode laser therapy or retinal cryoexy with normalization of the IOP are referred to a general ophthalmologist for continued follow-up. Fluorescein angiography is not routinely performed to control for ischaemic status at baseline as PRP or retinal cryoexy only is considered for CRVO patients in the occurrence of a NE. Information was collected at baseline and then yearly until the end of follow-up up to 5 years.

Statistical analyses

For statistical analyses, the independent Student t-test was used for continuous variables and Pearson’s chi-squared test for categorical data.

Results

During the study period, 243 patients presented with CRVO. In 72/243 (30%) patients, NE was observed at baseline or during the follow-up. These 72 patients with NE constituted the study group. Demographic and baseline characteristics are listed in Table 1.

Neovascularization

In 23/72 (32%) eyes, there was evidence of NE at baseline (early NE group) while 28/72 (39%) eyes developed NE after discontinuation of intravitreal therapy for ME (late NE group). The remaining 21/72 (29%) eyes did not have ME and were therefore not given intravitreal injections. This group showed evidence of NE after a mean time of 3.9 ± 4.3 months while the median time was 2 months (late NE group). In the patients that developed NE after discontinuation of intravitreal therapy for ME, the mean time to NE was 15.6 ± 13.8 months from the baseline visit and 4.1 ± 2.6 months from the last injection. Patients treated with an intravitreal dexamethasone implant (n = 11) developed NE earlier at 3.2 ± 1.9 months compared to patients treated with anti-VEGF injections (n = 17) where NE occurred at 4.7 ± 2.9 months (p = 0.10) (Fig. 1). In the early NE group, 6/23 (26%) eyes had NVI/NVA while 17/23 (74%) eyes had NVG at baseline. Overall, NVI/ NVA occurred in 19 patients (26%) and NVG was observed in 53 patients (74%) at the last follow-up (Table 2).

Time of follow-up

Time of follow-up is illustrated in Fig. 2. Patients in the early NE group were...
followed for a mean of 14.9 ± 2.9 months (range 2—51) compared to 32.9 ± 2.9 months (range 1—60) in the late NE group (p < 0.001). During the five-year period, 12 patients were lost to follow-up (9 lost and 3 deceased). A total of 54 patients were dismissed from follow-up. Forty-nine due to inactive disease, 3 because of low visual acuity and 2 for other reasons. At 5 years, 6 patients were still in follow-up.

Visual outcome

Overall, the BCVA in the study group decreased by 13.5 ETDRS letters from 21.8 letters at baseline to 8.3 letters at the end of follow-up (p < 0.001). The BCVA in the early NE group decreased by 2.3 ETDRS letters to 8.6 letters (p = NS) and in the late NE group by 18.8 letters to 8.1 letters (p < 0.001). The difference in BCVA between the groups was not significant at the end of follow-up (p = NS). At the last visit, 53/72 (74%) of all eyes had a BCVA of counting fingers (CF) or less respectively 18/23 (78%) in the early NE group and 35/49 (71%) in the late NE group (p = NS). In Snellen equivalent, the BCVA decreased from 20/360 at baseline to 20/570 at the end of follow-up. Only 7/72 (10%) eyes had a BCVA of 20/200 or better, 3/23 (13%) in the early group and 4/49 (8%) in the late group (p = NS).

Treatment exposure: In the early NE group, the patients received a mean of 1.1 ± 2.7 intravitreal injections compared to 5.2 ± 5.7 intravitreal injections in the late NE group until the end of follow-up. There were no differences in treatment patterns regarding PRP, cyclodiode laser therapy and retinal cryopexy between the study groups (Table 2). The most common treatment for NE was PRP or PRP combined with adjuvant anti-VEGF therapy (Table 3). Patients treated with adjuvant anti-VEGF injections combined with PRP as initial treatment for NE (n = 23) were more likely to receive a pressure-lowering procedure compared to patients starting with PRP alone (n = 31). Of the patients receiving initial PRP combined with adjuvant anti-VEGF therapy, 15/23 (65%) received subsequent cyclodiode laser therapy compared to 10/31 (32%) of the patients treated with PRP only (p = 0.016). The baseline intraocular pressure (IOP) was significantly higher in the adjuvant group 38.0 ± 15.7 mmHg compared to 29.4 ± 11.6 mmHg in the group treated initially with PRP only (p = 0.031). The IOP at the onset of NE had a significant impact on the need for additional pressure-lowering procedures. Of the patients presenting with an IOP of less than 30 mmHg, only 3/29 (10%) needed subsequent cyclodiode laser therapy compared to 35/43 (81%) patients with a baseline IOP higher than 30 mmHg (p < 0.001) (Table 4).

Discussion

Neovascular glaucoma is a severe and common complication of ischaemic CRVO. In our study, we found that almost a third of the patients developed a neovascular event at some stage during the follow-up. In a large prospective study with both ischaemic and non-ischaemic CRVO patients, Hayreh found that the cumulative probability of developing NVI was 14% (Hayreh and Zimmerman, 2012). Chen observed that 22% of CRVO patients developed NVI (Chen et al., 2014). In our study, substantially more patients (30%) developed a neovascular complication. It is hard to compare the occurrence rate of NE between different studies. The development of NE depends on the baseline characteristics of the patients included in the analysis. Ischaemic status, age and
At onset of NE.

growth factor.

Intraocular pressure last visit mmHg (n/C6)

Intraocular pressure at onset* mmHg (n/C6)

Retinal cryopexy

Cyclodiode laser

nPRP

Neovascular glaucoma

Neovascularization of iris/angle

Intravitreal injections mean (±SD)

PRP n (%) of patients

Cyclodiode laser n (%) of patients

Retinal cryopexy n (%) of patients

Adjuvant anti-VEGF injection n (%) of patients

Intraocular pressure last visit mmHg (±SD)

NE = neovascular event, PRP = panretinal photocoagulation, VEGF = vascular endothelial growth factor.

NE = neovascular event.

Table 2. Neovascular characteristics and treatment exposure at last visit.

| Parameter | Early NE | Late NE | p |
|-----------|----------|---------|---|
| Neovascular glaucoma n (%) | 20 (87) | 33 (67) | 0.08 |
| Neovascularization of iris/angle n (%) | 3 (13) | 16 (33) | 0.08 |
| Intravitreal injections mean (±SD) | 1.1 ± 2.7 | 5.2 ± 5.7 | <0.001 |
| PRP n (%) of patients | 16 (70) | 40 (82) | NS |
| Cyclodiode laser n (%) of patients | 15 (65) | 23 (46) | 0.15 |
| Retinal cryopexy n (%) of patients | 12 (52) | 20 (45) | NS |
| Adjuvant anti-VEGF injection n (%) of patients | 10 (44) | 25 (51) | NS |
| Intraocular pressure at onset* mmHg (±SD) | 41.4 (10.3) | 31.8 (14.4) | 0.002 |
| Intraocular pressure last visit mmHg (±SD) | 22.0 (13.7) | 16.9 (8.9) | NS |

Table 3. Initial treatment for neovascular event.

| Treatment modality | n = 72 |
|--------------------|--------|
| PRP | 31 |
| PRP and anti-VEGF | 23 |
| Retinal cryopexy and cyclodiode laser | 7 |
| Cyclodiode laser | 3 |
| Retinal cryopexy, cyclodiode laser and anti-VEGF | 2 |
| Retinal cryopexy | 1 |
| Cyclodiode laser and anti-VEGF | 1 |
| Declined treatment | 4 |

PRP = panretinal photocoagulation, VEGF = vascular endothelial growth factor.

comorbidities all affect the development of neovascular complications and will vary in different cohorts. A difference in baseline characteristics between studies may explain the difference in NE. In the study by Chen, patients with NVI at baseline were excluded from the analysis (Chen et al., 2014).

Applying the same exclusion criteria, only 22% developed a neovascular event in our study. Preexisting primary open-angle glaucoma has been found to be a risk factor for developing NVG (Hayreh and Zimmerman, 2012; Chen et al., 2014). Compared to the previous papers, the patients in our study were more than 10 years older at baseline and had a higher percentage of risk factors like glaucoma and hypertension. This may explain the higher rate of NE in our analysis.

Significantly, more patients had pre-existing glaucoma and ocular hypertension (OHT) in the NE groups compared to patients in the control group. In our study, 46% in the NE groups and 22% in the control group had glaucoma/OHT. In a previous study, a prevalence of approximately 25% of preexisting glaucoma/OHT has been reported (Hayreh et al., 2004). In a subgroup analysis in that study, patients over 75 years old had a 42% prevalence of glaucoma/OHT. This is similar to our NE groups that had a mean age of 80.1 years. The patients in our control group were 70.2 years old, significantly younger than the NE groups but at a similar age to the patients in the Hayreh study.

Interestingly, a substantial part of the patients presented with NVG already at their first visit. Classically, the incidence of NVG increases steeply during the first months and will peak between 4 and 6 months after disease onset (Hayreh and Zimmerman, 2012). However, NVG has been reported to occur anywhere between 2 weeks and 2 years after the onset of ischaemic CRVO (Ramakrishnan et al., 2013). In our patients that had NE at baseline, the period between onset of CRVO and presentation with symptoms is uncertain. These patients were significantly older and had more comorbidities like glaucoma and arterial hypertension compared to patients developing NVG at a later stage. Hypothetically, an elderly patient with an eye already affected by advanced glaucoma may not always notice the symptoms of a new CRVO, due to low preexisting visual function, and will first seek medical care for other reasons or when a red painful eye secondary to NVG develops. There is a paucity of reports in the literature that NVG can be seen already at the baseline visit, but our real-life data suggest that this entity is not rare.

The visual prognosis in patients with NE secondary to CRVO is very poor. At the end of follow-up, almost three quarters of the patients had a BCVA of CF or less. We did not find that initial intravitreal injections improved the visual outcome in patients that subsequently developed NE. Patients in the late NE group that had received previous intravitreal injections had the same poor visual outcome as patients in the
early NE group. The decrease in BCVA occurred concomitantly with the development of the NE, and thus, a plausible cause for the vision loss is increased macular ischaemia. In a recent study that investigated the onset of NVG in patients treated with intravitreal anti-VEGF injections, three quarters of the patients had a final BCVA of 20/400 or less (DeCroos et al., 2014).

The occurrence of NE was delayed in patients that were treated with intravitreal injections compared to the natural history. In this subgroup, the mean time to the development of NE was around 15 months after the baseline visit. However, NE occurred promptly after a mean time of 4 months when the injections were discontinued. This is comparable to the onset of NE previously reported in treatment-naive ischaemic CRVO patients (1993; Hayreh and Zimmerman, 2012). Intravitreal injections may temporarily change the pathophysiology of CRVO and postpone the occurrence of NVG. When treatment is discontinued in patients with ischaemic CRVO, the neovascular clock starts running and the neovascular complications appear temporally in a similar manner to the natural history in non-treated ischaemic eyes. Both eyes treated with Ozurdex and anti-VEGF injections developed NE after treatment was stopped. In patients that previously received Ozurdex therapy, neovascularization was observed earlier than in anti-VEGF-treated subjects. However, this result was not significant. The small sample size may have affected this outcome.

Several studies have previously shown that adjuvant anti-VEGF injections cause a fast resolution of anterior chamber neovascularization (Avery, 2006; Yazdani et al., 2007). However, the effect of anti-VEGF injections to treat NVG is temporary and lasts generally for less than 8 weeks (Wakabayashi et al., 2008). In our study, we found that patients treated with adjuvant anti-VEGF therapy for NVG were more likely to need a subsequent IOP-lowering procedure. The patients treated with adjuvant anti-VEGF injections had a significantly higher pressure at baseline, which may represent a more advanced neovascular process needing a more aggressive therapeutic approach. Baseline IOP at the diagnosis of NE seems to be an important factor in anticipating the need for a future pressure-lowering procedure. More than 80% of the patients presenting with a pressure over 30 mmHg needed cyclodiode laser therapy at some stage of the follow-up. This procedure is often done several months after the diagnosis, and this delay in treatment with continuous high pressure may cause additional damage to the optic nerve. An early intervention that reduces the IOP quickly may be beneficial for these patients of whom many already have optic nerve damage secondary to glaucoma before the onset of CRVO. Patients presenting with NVI/NVA can usually be managed successfully with PRP. No patients in our material presenting with NVI/NVA needed pressure-lowering surgery at any stage of the follow-up. The therapeutic window for preventing NVG is unfortunately narrow. This highlights the importance of a very close follow-up in ischaemic eyes at the onset of the disease and when treatment is discontinued.

There are several limitations to this study. The weakness of a retrospective cohort study is that many physicians and other healthcare professionals are involved in the follow-up, increasing the possibility of non-uniform assessments and measurements. The follow-up and treatment decisions were at the physician’s discretion and did not follow a standardized protocol. However, this is the essence of common practice and we believe that a real-life setting can give important information of outcomes outside the strict controlled conditions in a randomized trial.

In conclusion, NVG is a common complication of CRVO and quite many CRVO patients present with a neovascularization at the first visit. Treatment with intravitreal injections for ME does not improve the visual outcome in patients that subsequently will develop NE. The onset of NE after the discontinuation of intravitreal therapy will follow a time–course similar to patients with ischaemic CRVO not treated with intravitreal injections. A high baseline IOP predicts the need for subsequent pressure-lowering procedures.

References
Avery RL (2006): Regression of retinal and iris neovascularization after intravitreal bevazcizumab (Avastin) treatment. Retina 26: 352–354.
Brown DM, Heier JS, Clark WL et al. (2013): Intravitreal adalimumab injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. Am J Ophthalmol 155: 429–437.e247.
Brown DM, Wykoff CC, Wong TP, Mariani AF, Croft DE & Schuetzle KL (2014): Ranibizumab in preproliferative (ischemic) central retinal vein occlusion: the rubesis anti-VEGF (RAVE) trial. Retina 34: 1728–1735.
Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, Murahashi WY & Rubio RG (2011): Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmolgy 118: 2041–2049.
Central Vein Occlusion Study Group (1993): Baseline and early natural history report. The Central Vein Occlusion Study. Arch Ophthalmol 111: 1087–1095.
Chen HF, Chen MC, Lai CC et al. (2014): Neovascular glaucoma after central retinal vein occlusion in pre-existing glaucoma. BMC Ophthalmol 14: 119.
DeCroos FC, Todorich B, Alshareef R, Khuthaila M, Fekrat S, Ho AC, Regillo CD & Spirn MJ (2014): Neovascular events in eyes with central retinal vein occlusion undergoing serial bevazcizumab or ranibizumab intravitreal injections: a retrospective review. J Ophthalmic Vis Res 9: 461–468.
Epstein DL, Algever PV, von Wendt G, Seregard S & Kvanta A (2012): Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study. Ophthalmolgy 119: 1184–1189.
Hayreh SS (1983): Classification of central retinal vein occlusion. Ophthalmology 90: 458–474.
Hayreh SS & Zimmerman MB (2012): Ocular neovascularization associated with central and hemiretinal vein occlusion. Retina 32: 1553–1565.
Hayreh SS, Zimmerman MB, Beri M & Podhajsky P (2004): Intraocular pressure abnormalities associated with central and hemiretinal vein occlusion. Ophthalmology 111: 133–141.
Iliev ME, Domig D, Wolf-Schnurrbursch U, Wolf S & Sarra GM (2006): Intravitreal bevacizumab (Avastin) in the treatment of neovascular glaucoma. Am J Ophthalmol 142: 1054–1056.

Ramakrishan RKS & Khurana M, Robin AL (2013): Diagnosis and management of glaucoma. JP Medical.

Rezar-Dreindl S, Eibenberger K, Polleisz A et al. (2017): Effect of intravitreal dexamethasone implant on intra-ocular cytokines and chemokines in eyes with retinal vein occlusion. Acta Ophthalmol 95: e119–e127.

Ryu CL, Elfersy A, Desai U, Hessburg T, Edwards P & Gao H (2014): The effect of anti-vascular endothelial growth factor therapy on the development of neovascular glaucoma after central retinal vein occlusion: a retrospective analysis. J Ophthalmol 2014: 317694.

Sasamoto Y, Oshima Y, Miki A, Wakabayashi T, Song D, Matsushita K, Hamasaki T & Nishida K (2012): Clinical outcomes and changes in aqueous vascular endothelial growth factor levels after intravitreal bevacizumab for iris neovascularization and neovascular glaucoma: a retrospective two-dose comparative study. J Ocul Pharmacol Ther 28: 41–48.

Sohn HJ, Han DH, Lee DY & Nam DH (2014): Changes in aqueous cytokines after intravitreal triamcinolone versus bevacizumab for macular oedema in branch retinal vein occlusion. Acta Ophthalmol 92: e217–e224.

Wakabayashi T, Oshima Y, Sakaguchi H et al. (2008): Intravitreal bevacizumab to treat iris neovascularization and neovascular glaucoma secondary to ischemic retinal diseases in 41 consecutive cases. Ophthalmology 115: 1571–1580. 1580.e1571-1573.

Wolf A, von Jagow B, Ulbig M & Haritoglou C (2011): Intracameral injection of bevacizumab for the treatment of neovascular glaucoma. Ophthalmologica 226: 51–56.

Yazdani S, Hendi K & Pakravan M (2007): Intravitreal bevacizumab (Avastin) injection for neovascular glaucoma. J Glaucoma 16: 437–439.

Received on July 5th, 2019. Accepted on May 14th, 2020.

*Correspondence: Manuel Casselholm de Salles Karolinska Institutet St. Erik Eye Hospital Polhemsgratan 50 11282 Stockholm Sweden Tel +4686723000 Fax +4686521216 E-mail: manuel.casselholm.de.salles@ki.se

The first and third author has received lecture fees for speaking at courses for Allergan, Bayer and Novartis during the past year. There are no other sources of conflict of interest.