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RETINAL DISORDERS

Intravitreal ranibizumab (Lucentis) for treatment of central retinal vein occlusion: a prospective study

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Abstract
Background/Purpose To evaluate the effect of individualized repeated intravitreal injections of ranibizumab (Lucentis) on visual acuity (VA) and central foveal thickness (CFT) for central retinal vein occlusion (CRVO)-induced macular edema.
Methods Our study was a prospective interventional case series. Twelve eyes of 12 consecutive patients diagnosed with CRVO-related macular edema (nine perfused, three ischemic CRVO) treated with repeated (when CFT was >220 μm) intravitreal injections of ranibizumab as a monotherapy within 3 months of onset were evaluated. Optical coherence tomography (OCT) and fluorescein angiography (FA) were performed monthly and every 3 months respectively. Changes in VA (ETDRS) and CFT were analyzed using the student's paired *t*-test.
Results The mean time from diagnosis until injection was 80 days (2.7 months; range, 63–90 days) and the follow-up time was 12 months. In total, 89 injections were performed (mean 7.4). The mean CFT improved from 480±166 μm at baseline to 230±33 μm ($P<0.001$) at the end of the follow-up. During the same period, of the 12 eyes, eight demonstrated improved VA (>0.3 LogMAR change, >15 letters), three stable VA and one worse VA as compared to baseline. None of the nine patients with perfused CRVO were converted to ischemic at 12 months, and one of the three eyes with ischemic CRVO developed iris neovascularization despite two ranibizumab injections. No ocular or systemic side-effects were noted.
Conclusion Individualized repeated intravitreal injections of ranibizumab have shown promising results in VA improvement and decrease in CFT in patients with macular edema associated with CRVO. Further studies are needed in order to elucidate the role of intravitreal lucentis in the ischemic form of CRVO, and its efficacy in preventing conversion from the perfused to the ischemic form of the disease.

Keywords Lucentis · Ranibizumab · CRVO · Intravitreal injection

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Introduction

Central retinal vein occlusion (CRVO) is a well-reported clinical entity that is a common cause of vision loss in the elderly, often as the result of macular edema and/or retinal ischemia [1]. Therefore, therapeutic approaches primarily aim to either manage macular edema or to prevent complications associated with retinal ischemia such as neovascularization and neovascular glaucoma. The Central Vein Occlusion study [2] failed to demonstrate statistically significant visual acuity benefit from grid laser photocoagulation for macular edema, and treatments such as intravitreal injections of triamcinolone acetonide (TA), though

initially promising [3, 4], were not proved beneficial in terms of visual acuity improvement at 1 year of follow up [5–9]. In addition, treatments with repeated intravitreal injections of TA have been linked with high complication rates, such as cataract formation and intraocular pressure rise [5–9]. Unfortunately, there is no other proven therapy for refractory macular edema due to CRVO, and the effort for investigating new treatment modalities is continuous and still ongoing.

Hypoxia-induced expression of vascular endothelial growth factor (VEGF) is though to be, at least partly, a trigger for macular edema, and high intravitreal levels of VEGF have been found in patients with retinal vein occlusion [10]. Upregulation of VEGF is associated with breakdown of the blood–retina barrier, with increased vascular permeability resulting in retinal edema, stimulation of endothelial cell growth and neovascularization [11–14]. In addition, it has been clinically suggested that VEGF could be a stimulus for retinal thickening, a conclusion that is supported by the improvement in foveal thickness that is achieved with repeated injections of ranibizumab in diabetic patients [15].

In accordance with the above theory, pharmacologic inhibition of VEGF has recently been tried using bevacizumab, a monoclonal antibody that is formulated for intravenous infusion and is off-label for intraocular use. Published studies have demonstrated promising results in visual acuity and retinal thickness in retinal vein occlusion-related edema [16–21]. Although recent studies [22–24] have shown similar results with the use of intravitreal ranibizumab, the exact benefit as well as the treatment pattern remain under ongoing research. So far, existing data are limited either to short-term studies, case series that follow a rigid injection scheme, or longer prospective studies with a more heterogeneous patient group.

Our study was designed based on specific inclusion criteria capable of creating a homogenous patient group that would be treated with a flexible injection scheme with re-injections depending on CFT. The patients were treated as a monotherapy with intravitreal ranibizumab, a fragment of a recombinant, humanized monoclonal antibody Fab that has been approved by the Food and Drug Administration (FDA) for intraocular use and has been shown to be beneficial in repeated doses in exudative age-related macular degeneration according to ANCHOR and MARINA studies [25, 26]. Long-term follow-up data over a period of 1 year are presented for the first time in a group following that specific treatment pattern as a monotherapy.

Materials and methods

Study design

The current study was designed as a prospective, consecutive, noncomparative case series. Informed consent was obtained from all patients. The study had Institutional Research Board approval. The study group was composed of those patients who met the eligibility criteria. Inclusion criteria were: a) age older than 18 years, b) patients with central retinal vein occlusion (perfused or non-perfused) confirmed with fluorescein angiogram (FA) of less than 3 months duration, and c) central foveal thickness (CFT) of more than 220 μm. Patients were excluded from the analysis if they had undergone any other treatment for CRVO such as intravitreal triamcinolone injection, radial optic neurotomy, or Argon laser photocoagulation since the time of onset of symptoms of CRVO, or if the duration of CRVO was more than 3 months. Patients with any co-existent ocular disease or previous intraocular surgery (apart from cataract surgery 6 months before their initial presentation) and/or ocular (intravitreal, peri- or parabulbar, sub-Tenon's) injection were also excluded from the study. In addition, within the exclusion criteria were pregnancy and uncontrolled hypertension.

Initially, each patient underwent best-corrected distance visual acuity (BCVA) measurement with the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, clinical examination including slit-lamp biomicrosopy, intraocular pressure (IOP) measurement using Goldman applanation tonometry, and indirect fundus examination. Baseline CFT was measured with optical coherence tomography (OCT) using the macular thickness map OCT pattern (STRATUS OCT, Carl Zeiss Meditec, Inc.). Each eye had a baseline fluorescein angiogram (FA) that was obtained by injection of 2 ml of 25% sodium fluorescein solution in the antecubital vein. Eyes were considered ischemic by FA if they had no observable neovascularization of the iris (on clinical examination or angiography) and had ten or more disk areas of nonperfusion. In all patients, intravitreal ranibizumab injection was performed.

Injection technique

Informed consent was obtained, and after the application of a sterile drape, ranibizumab was inserted through the pars plana 3.5 to 4.0 mm posterior to the surgical limbus using a 30-gauge needle.

Follow-up and treatment utility

Patients were examined every month following the intravitreal injection. Examination included BCVA measurement, IOP measurement and indirect fundus examination. All patients underwent monthly OCT scans measuring CFT, and FA every 3 months. Repeated intravitreal injections were performed when CFT appeared more than 220 μm on OCT.

Study endpoints

The primary study endpoint was the mean change in BCVA from baseline to 12 months. The secondary endpoints

included mean change in BCVA and CFT from baseline to 3 and 6 months, the incidence of ocular and systemic side-effects, the rate of progression to ischemic CRVO, and the effect of ranibizumab on ischaemic CRVO.

Statistical analysis

All data were collected in an MS-Excel 2004 spreadsheet and analyzed using SPSS 14.0 for Windows (SPSS Inc, Chicago, IL, USA). The visual acuity measurements were converted to logarithm of the minimum angle of resolution (logMAR) units in order to facilitate statistical manipulation. The paired-sample *t*-test was used to compare data. A P value of<0.05 was considered significant.

Results

Twelve eyes of 12 consecutive patients with macular edema associated with CRVO were treated with intravitreal ranibizumab. There were ten men and two women. The mean age of the patients at the time of the first injection was 63 years (range, 55–77 years). The mean time from diagnosis until injection was 80 days (2.7 months; range, 63–90 days) and the follow up time was 12 months. In total, 89 injections (mean 7.4) were performed (60 injections during the first 6 months [mean 5.0] and 29 injections during the last 6 months [mean 2.4]).

All patients had clinical evidence of CRVO including intraretinal hemorrhages and dilated, tortuous retinal veins in all four quadrants. All of the eyes had cystoid macular edema confirmed by OCT at baseline, and none of our patients had longstanding symptoms of CRVO before the diagnosis was made. Three of 12 CRVO cases were identified as ischemic according to the previously mentioned criteria, and one of three patients with non-perfused CRVO developed iris rubeosis with neovascular glaucoma 3 months from the first injection, following a total of two injections. An Ahmed valve had to be surgically inserted in order to control IOP, after panretinal photocoagulation was performed (Table 1). The baseline characteristics included a mean visual acuity of 32.50 ETDRS letters $(\log \mathrm{MAR} = 1.53 \pm 0.08)$ and a mean central retinal thickness of 480±166 μm.

One-, three- and six-month outcomes

At 1-month follow-up, visual acuity improved to a mean of 37.92 letters $(\log \mathrm{MAR} = 1.37 \pm 0.73)$, a difference from baseline that was not statistically significant (P=0.1). Mean post-treatment central retinal thickness at 1 month follow-up was 381±165 μm. The change in macular thickness as compared to baseline was statistically non-significant (borderline P=0.055).

Table 1 Summary of data for patients treated with intravitreal injections of ranibizumab for CRVO

Patient		1	2	3	4	5	6	7	8	9	10	11	12
Age (years)		55	56	56	59	59	59	63	64	68	69	75	77
Sex		Male	Male	Male	Male	Female	Male	Male	Male	Male	Male	Female	Male
Condition		CRVO	Ischemic	CRVO	CRVO	Ischemic	CRVO	CRVO	CRVO	CRVO	CRVO	Ischemic	CRVO
BCVA	Baseline	20/1600	HM	20/200	20/8000	20/400	20/200	20/200	20/100	20/200	20/200	20/800	20/100
	1 month	20/800	HM	20/200	20/8000	20/400	20/200	20/200	20/100	20/63	20/200	20/800	20/100
	3 months	20/800	20/1600	20/200	20/800	20/200	20/200	20/200	20/200	20/63	20/200	20/800	20/100
	6 months	20/800	20/800	20/63	20/800	20/200	20/200	20/200	20/200	20/40	20/200	20/800	20/200
	Final	20/800	20/800	20/63	20/400	20/200	20/63	20/200	20/200	20/32	20/200	20/800	20/100
CFT	Baseline	>600	>600	315	548	>600	275	580	550	>600	310	306	280
	1 month	540	>600	300	>600	540	240	320	195	240	335	291	275
	3 months	380	495	250	483	380	255	298	230	189	305	290	250
	6 months	240	335	210	325	240	230	220	320	170	240	295	290
	Final	254	281	195	275	254	220	235	207	164	235	230	210
Follow-up (months)		12	12	12	12	12	12	12	12	12	12	12	12
No of injections		7	4	6	11	9	6	6	8	5	9	8	10

[a] CRVO = central retinal vein occlusion, BCVA = best-corrected visual acuity, CFT = central foveal thickness.

At 3-month follow-up, visual acuity improved to a mean of 42.08 letters ($\log \mathrm{MAR} = 1.15 \pm 0.41$, $\mathrm{P} = 0.02$) and retinal thickness to a mean of 317±97 μm (P=0.003). At 6 months post-treatment with intravitreal ranibizumab injections, visual acuity improved to a mean of 45 letters (logMAR=1.1±0.4, P=0.017) and retinal thickness to a mean of 259±52 μm (P=0.001). CFT appeared less than 220 μm in three of the 12 patients.

End of follow-up outcomes

The last follow-up visit following treatment occurred at the 12-month visit after the start of treatment. The mean visual acuity was 50 ETDRS letters ($\log \mathrm{MAR} = 1.0 \pm 0.4$), a statistically significant change compared to baseline (P=0.006) and the mean retinal thickness improved to 230±33 μm (highly significant, P<0.001). A total of 89 injections (mean 7.4) of ranibizumab were performed at the end of the follow-up period. There was a statistically significant difference in mean BCVA and CFT (P=0.007 and P=0.008 respectively) when the first 6 months (mean number of injections=5.0) and the last 6 months (mean number of injections=2.4) were compared (the mean CFT and VA values during every month within the period of the first 6 months were compared with the respective values during the last 6 months). Of the 12 eyes, eight had improved visual acuity (more than 0.3 logMAR change, >15 letters), three had stable visual acuity and one worse visual acuity as compared with baseline. None of our patients developed cilioretinal collaterals in the optic disc, and neovascularization developed in only one patient 3 months after the initial injection. CFT appeared less than 220 μm in five of the 12 patients (two of them were the same patients with CFT<220 μm at the 6-month follow-up visit). At the end of the follow-up and 2 months after the last injection, one of the three patients with CFT<220 μm at the 6-month follow-up visit showed a minor increase of 10 μm in CFT (Table 1) without a respective change in VA. Also, none of the perfused CRVOs were converted to ischemic.

There was no intraocular pressure rise, ocular inflammation (such as uveitis), endophthalmitis, retinal detachment or tear, hypertension or any other systemic adverse events due to the ranibizumab injection.

Discussion

In this prospective study of consecutive CRVO patients with macular edema treated with intravitreal ranibizumab within a mean of 80 days (2.7 months) of onset, visual acuity appeared improved and macular edema decreased at the end of the follow-up period (12 months) when compared to baseline.

Hsu et al. [21], in a retrospective analysis of 30 eyes, suggested that visual acuity improved and macular edema decreased after a single injection of bevacizumab in the majority of treated patients as early as the 1-week visit.

In our study, the 1-month follow-up post treatment with a single injection of ranibizumab did not reveal a statistically significant change in visual acuity and macular thickness. Of course, the small number of patients in our study may be limiting in statistically detecting such a change. Another possible explanation could be either that eyes did not have an initial improvement in vision after a single injection, or that they may have had an improvement during the first weeks, with a relapse of macular edema towards the end of the first month due to the elapsed drug activity in the inner blood–retina barrier.

According to previous reports [28], in vascular retinal disorders with disruption of the inner blood–retina barrier (e.g. diabetic retinopathy), visual acuity appears to be altered in proportion to CFT. Average central retinal thickness in the normal population has been reported to be 203±24 μm (mean±SD) using the Stratus OCT [27], and therefore in our study the primary criterion for repeated intravitreal injections was CFT more than 220 μm (~normal mean+1 SD) on OCT aimed at maintaining a normal anatomical profile in our patients. Of course, it is possible that such a "definition" may result in a higher number of injections since the previously mentioned criterion is satisfied by a sizeable number of normal eyes. Nonetheless, previous published studies [16–21] using bevacizumab (Avastin) for treatment of the CRVO-induced macular edema report CFT>220 μm in all patients at the end of the follow-up period. In our study, monthly intravitreal Lucentis injections resulted in CFT≤220 μm in three patients 6 months after the first injection, and in five patients at the last follow-up visit.

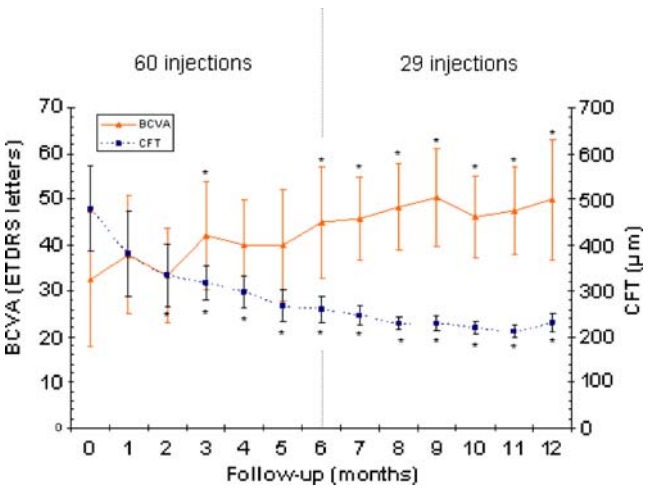

Fig. 1 Mean change in visual acuity and CFT over the follow-up period. Error bars represent mean and 95% confidence intervals. * Statistically significant change (P<0.05) as compared with baseline values. *BCVA* best-corrected visual acuity. *CFT* Central foveal thickness

A total of 60 injections (mean 5.0) was performed during the first 6 months and 29 injections (mean 2.4) during the last 6 months (total 89 injections, mean 7.4 in 12 months). The number of re-injections performed in our study appears to be higher than that reported in other reports using either intravitreal triamcinolone acetonide (TA) or intravitreal bevacizumab injections (ranging from a mean of 1.62 to 5.8 injections), but it appears to be similar to a recent prospective study that follows a similar injection scheme [24]. However, after repeated IVTA treatments the effect on reduction of retinal thickness and on the increase in visual acuity are reduced, and a high complication rate is associated with the repetitive nature of the treatment (significant intraocular pressure rise and cataract formation) [5–9].

Previous data suggested [21] that an injection of intravitreal bevacizumab has a limited beneficial effect of approximately 2 months, and that intermittent re-injections may be needed to sustain the visual benefits. Our data suggest that multiple injections with short intervals between them may have a cumulative effect on visual acuity and macular thickness, since a preservation of CFT on a lower and VA on a higher level is observed when the first 6 months (mean 5.0 injections) and the last 6 months (mean 2.4 injections) are compared (Fig. 1).

Recently, three prospective studies evaluating the effect of intravitreal ranibizumab on CRVO were published [22–24]. Spaide et al. [24] performed a 12-month follow-up prospective study with a flexible injection scheme similar to the one performed in our study, demonstrating a continuous improvement in VA with additional injections over the follow-up. The latter seems to agree with our findings. In addition, Pieramici et al. in a prospective study [22] treated the patients following a more rigid injection scheme (day 0, months 1, 2 and 3, and 3-monthly thereafter) arguing that the initial improvement in VA was not maintained between 3 and 6 months when the patients did not receive any injections, suggesting that an interval of 3 months between injections may be too long for most patients. Our data suggest that a

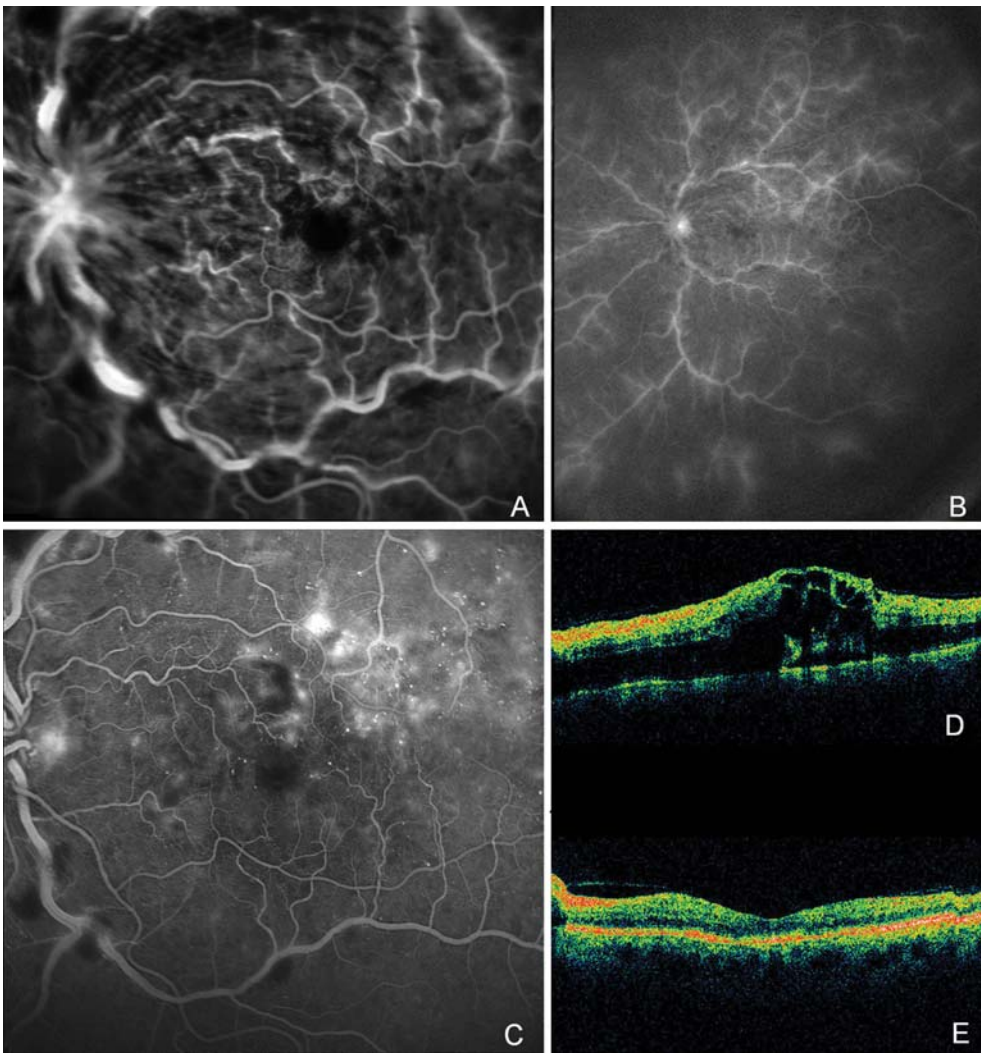

Fig. 2 Case 5. **a** FA of the left eye at presentation demonstrating remarkable distension of the retinal vessels, significant optic disc swelling, areas of non-perfusion and multiple intraretinal haemorrhages. **b** FA of the same patient at presentation using a Staurenghi 230 SLO lens. . The wide-field photo demonstrates areas of extensive non-perfusion in the periphery. Image has been inverted in order to match the rest of the Fig. 1 photos. **c** FA at 12-month follow-up visit. There is significant improvement, with resorption of haemorrages and resolution of disc swelling. **d** OCT of the same eye at presentation, demonstrating massive macular edema with cystoid spaces and intraretinal and subretinal fluid. CFT> 600 μm. **e** OCT 12 months after the initial presentation, showing profound decrease of macular thickness. CFT=254 μm

flexible injection scheme offers a more individualized treatment approach. Of course, the mean number of re-injections is higher overall (when CFT is used as a marker for repeated treatment), increasing the cost (especially when ranibizumab is used) and the potential complication risk. Nevertheless, in our series, we did not document any problems related to the repetitive nature of treatment, such as IOP rise, cataract formation or endophthalmitis.

Despite the non-comparative nature of our study, the natural history of patients with CRVO is well-documented and analyzed as part of the Central Retinal Vein Occlusion Study [29], according to which only 19% of patients with visual acuity worse than 20/200 at baseline exhibited VA improvement. Furthermore, Priglinger et al. [19] in their study reported that in the same VA group (<20/200), 42% of patients with CRVO-related edema treated with repeated injections of bevacizumab (Avastin) demonstrated improvement in VA to 20/200 or better. Although our study does not include an adequate number of patients to justify an accurate statistical comparison with the Retinal Vein Occlusion Study [29], we have to report that two out of six patients with visual acuity worse than 20/200 showed improvement of visual acuity at the end of the follow-up period. Also, at the end of the follow-up period CFT showed more than 50% reduction (as compared to baseline) in five out of six patients with VA worse than 20/400. In addition, anatomic improvement was profound in some cases (Figs. 2, 3 and 4).

In a retrospective analysis of six patients with macular edema due to CRVO treated with intravitreal bevacizumab, Ferrara et al. [20] reported no collateral formation, a fact that has been suggested to have occurred due to the absence of the need for improvement or maintenance of venous flow. In our series, none of our patients developed cilioretinal collaterals in the optic disc, and none of the cases exhibiting the non-ischemic form of CRVO was converted to ischemic.

Based on our data, interestingly, one out of three patients with ischemic CRVO developed iris neovascularization and neovascular glaucoma, despite the administration of two lucentis injections. Although this fact is difficult to define aetiologically, it is possible that the dynamic VEGF expression in the eye cannot be completely "intercepted" with ranibizumab, since the drug's half-life in the vitreous cavity appears to be only 9 days in patients with AMD [30]. Therefore, the latter raises questions about whether intravitreal lucentis administration is capable of preventing this complication in the ischemic form of CRVO. Another interesting observation is that all patients with ischemic CRVO demonstrated an improvement in VA of >15 letters, and the role of ranibizumab in this challenging form needs to be further elucidated. Furthermore, the fact that none of the nine patients with perfused CRVO has converted to ischemic at the 12-month follow-up point (when the rate of conversion has been reported to be 16% at 4 months following the initial diagnosis [31]) raises questions about whether this could be attributed to the repeated lucentis injections.

Our study has some obvious limitations. Our study sample was limited in number, and there was no control group for comparison of our data. However, the patients were treated within 80 days of the onset of symptoms only with the FDA-approved intravitreal ranibizumab (no other treatment had

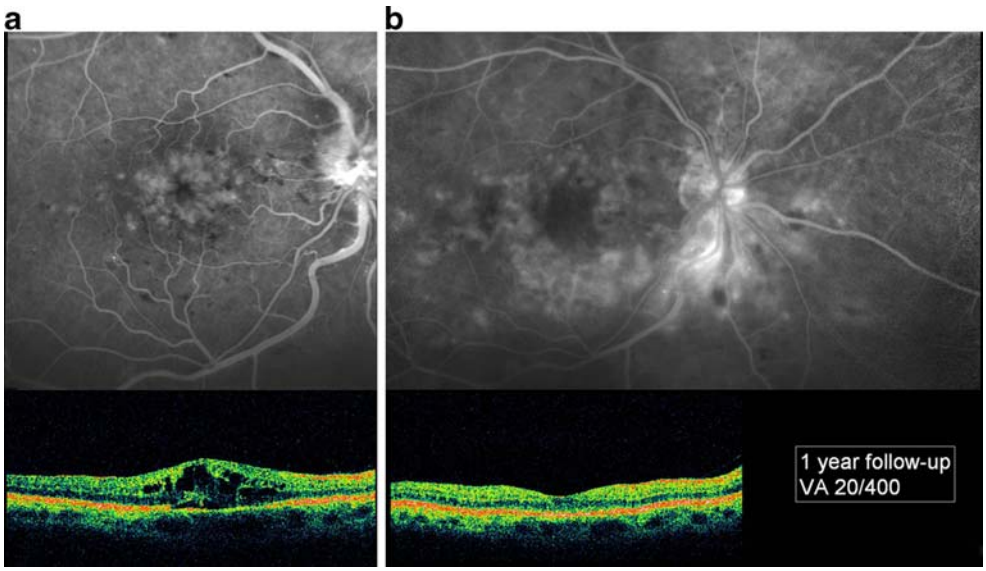

Fig. 3 Case 4. **a** FA of the right eye at presentation revealing significant macular edema, considerable optic disc swelling and venous tortuosity and dilatation. OCT demonstrates intraretinal fluid in cystoid spaces and minimal subretinal fluid. Visual acuity was 20/8000. **b** Same patient's FA and OCT at 12-month follow-up visit following a total of 11 intravitreal ranibizumab injections. Macular edema was significantly decreased (CFT=275 μm on OCT) ,and visual acuity improved to 20/400

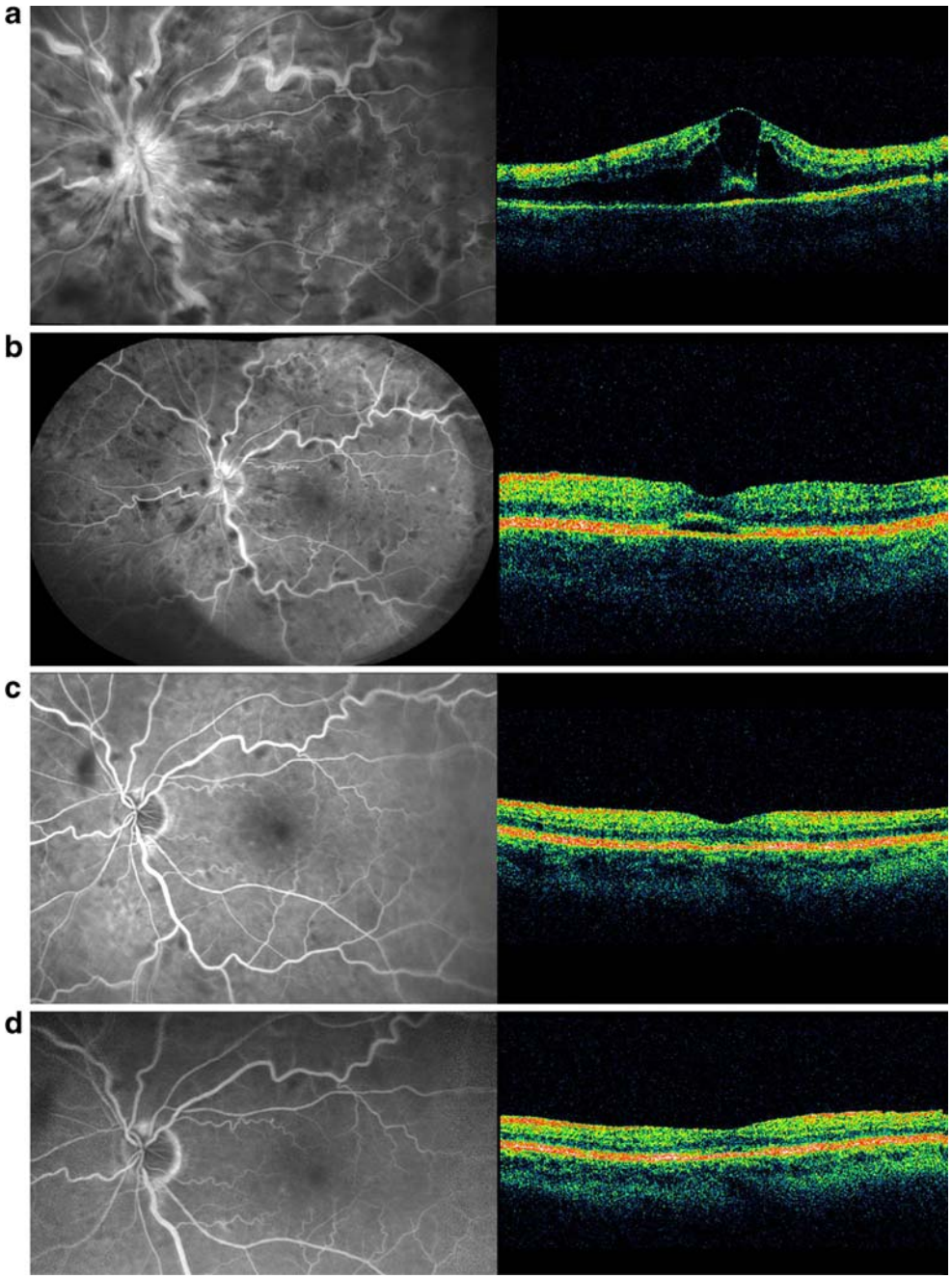

Fig. 4 Case 9. **a** FA and OCT of the left eye at first presentation, demonstrating optic disc hyperfluorescence (edema), remarkable tortuosity and dilatation of the retinal vessels and multiple haemorrhages. OCT showed remarkable sub- and intra-retinal fluid (CFT>600 μm). Visual acuity was 20/200. **b** Same case at 1-month follow-up visit following the first lucentis injection. There is marked improvement on FA and reduction of retinal thickness on OCT, with minimal residual sub-retinal fluid in the foveal area. **c** Same patient 5 months after the initial presentation, and following a total of four intravitreal ranibizumab injections. **d** End of follow-up period. There is profound anatomical improvement on FA and OCT (CFT=164 μm at this point). Visual acuity is 20/63

been previously instituted). Also, although limited in number, patients with ischemic CRVO were also included, and as previously mentioned one of them developed iris rubeosis despite the treatment with ranibizumab. Additionally, the treatment regimen included short intervals between injections and the follow-up period was 12 months. OCT and FA were performed monthly and every 3 months respectively. The treated patients showed anatomical and functional improvement without any systemic or ocular adverse events.

Overall, repeated intravitreal injections of ranibizumab have shown promising results in visual acuity improvement and decrease in macular thickness in patients with macular edema associated with CRVO. In addition, no ocular or systemic side-effects were demonstrated. Further studies are needed in order to prove the effect of ranibizumab treatment on CRVO patients, clarify the proper point for onset/end of treatment and standardize the frequency of intervals between injections. Also, it is interesting to elucidate its role in the ischemic form of CRVO, and specifically whether it is possible that intravitreal ranibizumab could reduce the rate of progression from perfused to non-perfused CRVO and prevent neovascular glaucoma in the ischemic cases.

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