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ORIGINAL PAPER

The influence of anti-VEGF therapy on present day management of macular edema due to BRVO and CRVO: a longitudinal analysis on visual function, injection time interval and complications

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Abstract The purpose of this study was to evaluate the impact of intravitreal bevacizumab injections on the management and outcome of patients affected by retinal vein occlusions, their effectiveness on morphological and functional parameters, the modalities of long-term management and the need for additional laser treatment due to ischemic retinal evolution. Patients diagnosed with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) had a comprehensive work-up including complete ophthalmic examination, fluorangiography (FA), optical coherence tomography (OCT), visual field testing (VFT), microperimetry (MP), and laser flare photometry (LFP). In case of BRVO, intraocular bevacizumab injection was performed if significant macular edema/visual deficit was still present 3 months after onset of occlusion and injections were started at presentation in case of CRVO. Post-injection follow-up examination including best corrected visual acuity (BCVA), intraocular pressure (IOP), LFP, OCT, MP, and VFT were performed monthly and recorded at the end of follow-up. Follow-up FA was performed between 12 and 18 months after diagnosis. Injections were repeated in case of recurrence of a significant central macular edema. Patients were subdivided into 2 groups according to number of injections: 1–4 injections or more than 4 injections. The proportion of resolved cases (no recurrence after a minimum follow-up of 12 months) was calculated and correlated with number of injections. In patients needing sustained injections, management modalities were recorded. The proportion of patients having needed laser photocoagulation treatment because of significant ischemic signs was recorded. Fifty-one patients were diagnosed with retinal vein occlusion between 2006 and 2012 at the Centre for Specialized Ophthalmic Care (COS) in Lausanne, Switzerland. Forty-four had enough data and were included in the study. Nine eyes were affected by CRVO and 35 were affected by BRVO. Mean BCVA at presentation was 0.24 ± 0.2 and improved to 0.81 ± 0.38 ($p < 0.01$) at 48 months. MP improved from 184.9 ± 92 to 362.5 ± 56.2 ($p < 0.01$) at 42 months follow-up. The number of injections varied from 1 to 25 (mean 5.5 ± 5.43). 31/44 eyes received 1–4 injections (group 1) of which all were recurrence free, with a follow-up of at least 1 years in all. 13/44 eyes received more than 5 injections (group 2) with functional and morphological parameters maintained in 9/13 but only 1/13 patients showed resolution. Rhythm of injection varied from one patient to another but 8/13 patients needing continuous injections had a constant time interval between injections. In 8/44 patients, laser

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photocoagulation had to be performed due to ischemic complications. The visual outcome using bevacizumab intravitreal injection was exceptionally good and functional parameters such as BCVA, MP, and VFT improved significantly. In about two-thirds of patients, resolution was obtained after 1–4 injections. In one-third of patients, continuous injections were necessary but a constant rhythm for re-injection for each patient could be established allowing to reduce to a minimum follow-up visits. The absence of significant side effects allowed to re-treat apparently without limitation achieving maintained visual function. FA monitoring for the detection of ischemic complications should not be neglected especially in cases where bevacizumab could be discontinued.

Keywords Branch retinal vein occlusion (BRVO) · Central retinal vein occlusion (CRVO) · Bevacizumab · Optical coherence tomography (OCT) · Microperimetry (MP) · Fluorescein angiography (FA) · Individual injection time interval

Introduction

Retinal vein occlusion (RVO), including central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), is one of the most common retinal vascular diseases in adults [1–3]. Branch RVO (BRVO) is the most common type of RVO while central RVO (CRVO) is less common, the latter presenting however a much more severe visual loss [3]. They both cause a painless loss of vision and the extent of decreased central vision is correlated to macular edema [4, 5].

The obstruction in venous outflow after CRVO and BRVO increases intraluminal venous pressure and causes retinal edema [6].

Management was twofold aimed: one side at reducing macular edema and one side at avoiding ischemic complications.

Standard management consisted of laser grid treatment to try to reduce macular edema.

However, this approach was only marginally efficient to obtain visual improvement.

The Branch Vein Retinal Occlusion Group pointed out an improvement of 1.33 lines after laser grid treatment compared to an improvement of 0.23 lines in the control group, leaving the patients with a substantial visual disability in the affected eye [4]. The central Vein Occlusion Study demonstrated, despite some reduction in macular edema, no visual benefit in the laser treatment group, compared to the control group, thus it was advised to observe rather than treat CRVO patients, watching for retinal or iris neovascularization [5].

Hence, BRVO benefitted from an unsatisfactory therapeutic management and no useful treatment was available for CRVO.

The frustration about inadequate therapy in such a frequent and visual impairing disease was such, that both, patients and doctors, were prone to attempt extremely invasive and delicate surgical interventions. The aim of surgery was to relieve the putative anatomic block caused by the lamina cribrosa in CRVO and the common adventitial sheath in BRVO.

With this aim in mind at the beginning of the century radial optic neurotomy was proposed for CRVO [7] and sheathotomy for BRVO [8].

Another surgical procedure tried in those years was retinal endovascular surgery (REVS). The procedure comprised in the cannulation of a major retinal vein branch with a fine needle directed toward the optic disc, followed by controlled infusion of tissue plasminogen activator (tPA) to dislodge or dissolve the thrombus from the central retinal vein and thereby relieve retinal venous congestion.

All surgical procedures were doomed by the technical challenge of the procedure itself and the high rate of intra and postoperative complications along with the scarce visual recovery [9].

Medical approaches were proposed, in the attempt to restore, at least partially, the circulation in the retina. Among those, isovolemic hemodilution involved the coordination with an internist to lower hematocrit to a range of 30–35 % via exchange of whole blood for plasma with dextran [10]. Unfortunately, also this approach had little effect on visual recovery.

The use of various systemic pharmacologic agents such as high-dose niacin, bioflavonoids, low-molecular-weight heparin, aspirin, other antiplatelet drugs, and Coumadin were only marginally effective on visual acuity [11].

In this context, several studies reported the attempt to use steroids in order to shut down the inflammatory signaling, which was thought to be the principal culprit for macular edema [12–16].

The initial enthusiasm regarding intraocular steroids was however hampered by the side effects related to its use, including propensity to produce ocular hypertension, glaucoma, and cataract, counterbalancing its beneficial effect [17–19].

The second management issue was to deal with ischemic complication of RVO.

In this regard, BRVO and CRVO were classically divided into ischemic and non-ischemic forms, a good indicative parameter to indentify severe disease with a high propensity to develop neovascularization in order to perform strict follow-up and eventually perform treatment of ischemic and neovascular complication [22].

The advent of intravitreal anti-VEGF therapy opened a new era in the treatment of RVO. In 2007, the first reports on the use of anti-VEGF to treat macular edema due to RVO were published and its effectiveness was immediately obvious [20, 21].

Not only were anti-VEGF agents active on retinal edema, but they also reduced neovascular complications due to ischemia.

Our aim was to analyze the influence of anti-VEGF therapy on the management of RVO with macular edema in a longitudinal study looking at functional outcomes such as visual acuity, visual filed testing, and microperimetry (MP) as well as morphological evolution using OCT.

Our study also addressed the crucial question regarding the need for repeated injection in a fairly important proportion of patients.

Patients and methods

Inclusion criteria

Charts of patients having received standard care at the Centre for Ophthalmic Specialised Care (COS), Lausanne, Switzerland for RVOs from 2006 to 2012 were identified.

A written consent was obtained from all patients and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Only patients with a follow-up of more than 1 year were included.

Work-up

Patients had a comprehensive work-up including complete ophthalmic examination, fluorescein angiography (FA), spectral domain optical coherence tomography (OCT), visual field testing (VFT), microperimetry (MP), and laser flare photometry (LFP).

A Topcon 50 IA camera (Tokjo, Japan), coupled to an ImageNet (Topcon) image digitalizing system or the Heidelberg Spectralis optical coherence tomography system (Heidelberg Engineering, Heidelberg, Germany) was used to acquire the FA images.

OCT was performed using OTI-Spectral OCT/SLO (OTI Inc, Toronto, Canada) or the Heidelberg Spectralis optical coherence tomography system (Heidelberg Engineering, Heidelberg, Germany) and MP was performed using the program Pattern Polar 3–11°, Size Goldmann III of the OTI-Spectral OCT/SLO microperimeter.

LFP assessment was performed using a Kowa FM-500 (Kowa Company, Ltd., Electronics and Optics Division, Tokyo, Japan) at each follow-up visit. For VFT, the G1 program of the OCTOPUS 900 (Octopus 900, G Standard; Haag-Strait International) was used.

BCVA was recorded in decimals.

Post-injection follow-up examinations including best corrected visual acuity (BCVA), intraocular pressure (IOP), LFP, OCT, MP, and VFT were performed monthly in multiple injected patients during the first 4 injections and three-monthly in patients controlled without injection and recorded at the end of follow-up. Follow-up FA was performed between 12 and 18 months after diagnosis and at least 12 months after the last injection of bevacizumab in order to detect significant ischemic areas and/or retinal neovessels, and proportion of patients needing laser treatment was recorded.

Standard care

Standard care consisted of intravitreal bevacizumab injection (2.0 mg) (IVB) in case of macular edema and a decrease of vision.

In case of BRVO, the first injection was performed if significant macular edema was still present 3 months after onset of occlusion and for CRVO injections were started at presentation.

Table 1 Characteristics of the CRVO patients included in the study

CRVO	7 (9 eyes)
Mean age at presentation	63.4 ± 22.9 years
Male/female	6/1
RE/LE involved	5/4
Bilateral cases	2
Mean BCVA at presentation	0.15 ± 0.10
Mean BCVA at last follow-up	0.66 ± 0.33
Mean follow-up	18.5 ± 7.9 months
Mean number of injections	3 ± 2.6

Table 2 Characteristics of the BRVO patients included in the study

BRVO	34 patients/35 eyes
Mean age at presentation	68.8 ± 10.3 years
Male/female	22/12
RE/LE involved	15/20
Bilateral cases	1
Mean BCVA at presentation	0.26 ± 0.20
Mean BCVA at last follow-up	0.84 ± 0.29
Mean follow-up	20.7 ± 9.4 months
Mean number of injections	4.2 ± 3.6

On follow-up visits, treatment was rendered whenever decrease of BCVA along with signs of active exudation at OCT was detected.

Outcomes

The number of injections per patient was recorded, and patients were divided into 2 groups according to the number of injections [1], 4 injections or less [2] and 5 injections or more, and evolution of functional parameters (BCVA, MP, and VFT) and morphological parameters (OCT) was recorded and correlated in these 2 groups.

Further, to determine the long-term evolution of cases, the proportion of resolutions (no injection for more than 12 months) and mean follow-up without injection were calculated. In the group with more than 4 injections, the mean time interval between injections was calculated not taking into account the 3 first injections considered as the loading period. Proportion of failures defined as persistence of edema not responding to two consecutive injections were recorded.

Table 3 Mean data of the 2 groups of patients for all functional parameters and retinal thickness

	Group 1	Group 2
BCVA at presentation	0.25 ± 0.20	0.26 ± 0.16
BCVA at 12 months	0.77 ± 0.31	0.78 ± 0.24
BCVA at 24 months	0.87 ± 0.23	0.75 ± 0.25
BCVA at 36 months	0.91 ± 0.2	0.7 ± 0.21
BCVA at 42 months	0.92 ± 0.17	0.6 ± 0.52
MD at presentation	9.25 ± 4.31	8.68 ± 2.86
MD at 12 months	4.5 ± 4.05	8.23 ± 4.75
MD at 24 months	4.77 ± 4.88	8.17 ± 3.74
MD at 36 months	4.47 ± 3.57	8.21 ± 2.94
MD at 42 months	4.47 ± 3.57	8.31 ± 3.21
MP values at presentation	184.94 ± 92.01	151.66 ± 43.39
MP values at 12 months	318.11 ± 93.14	243.55 ± 85.61
MP values at 24 months	311.85 ± 114.24	295.33 ± 68.83
MP values at 36 months	361.33 ± 38.14	329.22 ± 28.09
MP values at 42 months	359.31 ± 39.74	277 ± 52.32
OCT thickness at presentation	300.83 ± 101.39	749.23 ± 129.23
OCT thickness at 12 months	259.66 ± 109.8	242.44 ± 36.49
OCT thickness at 24 months	259.66 ± 109.79	239 ± 45.28
OCT thickness at 36 months	245.2 ± 55.54	219.66 ± 22.14
OCT thickness at 42 months	246.3 ± 31.56	229 ± 16.64

Group 1 4 injections or less: $N = 31$ eyes (27 BRVO, 4 CRVO)

Group 2 5 injections or more: $N = 13$ eyes (8 BRVO, 5 CRVO)

Results

51 patients were diagnosed with retinal vein occlusion and 44 eyes had enough data to be included in the study.

Nine eyes were affected by CRVO and 35 were affected by BRVO.

Tables 1 and 2 resume the characteristics of the patients affected by CRVO and BRVO.

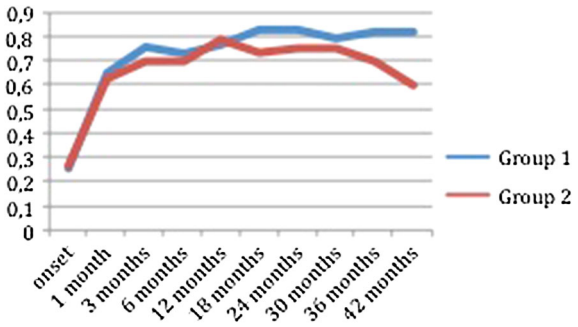

Fig. 1 Graph of VA values in the 2 groups from *onset* to 42 months of follow-up

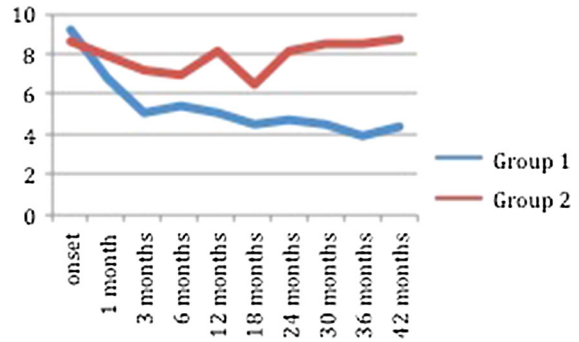

Fig. 2 Graph of mean defect (MD) values of VF in the 2 groups from *onset* to 42 months of follow-up

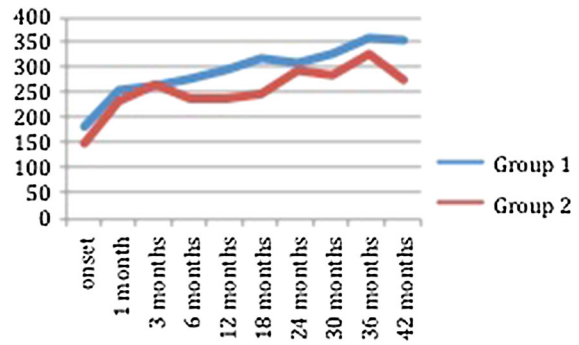

Fig. 3 Graph of microperimetry values in the 2 groups from *onset* to 42 months of follow-up

Subgroups according to number of injections

The entire set of patients (BRVO and CRVO) was subdivided into 2 groups, according to the number of injections needed to maintain retinal function.

The number of eyes per subgroup were as follows:

- *Group 1* 4 injections or less: $N = 31$ eyes (27 BRVO, 4 CRVO)
- *Group 2* 5 injections or more: $N = 13$ eyes (8 BRVO, 5 CRVO)

Visual acuity, visual field, MP, and OCT measurement of macular thickness were the parameters considered during the follow-up period within the 2 groups, the evolution of which interestingly did not differ significantly from each other. Table 3 resumes the mean data of the 2 groups for all functional parameters and retinal thickness.

Visual acuity

Mean BCVA in the entire group (BRVO and CRVO) at presentation was 0.24 ± 0.2 and improved to 0.81 ± 0.38 ($p < 0.01$) at 42 months. Mean BCVA at presentation was 0.15 (±0.10) in the CRVO group and 0.26 (±0.20) in the BRVO group and increased respectively to 0.59 (±0.31) and 0.79 (±0.32) at 12 months and to 0.61 (±0.37) and 0.89 (±0.32) at 18 months (Fig. 1).

Visual field testing

The visual field test measured an average mean defect value (MD) at presentation of 12.5 dB (±0.9) in the CRVO group and of 8.8 dB (±4.4) in the BRVO group that decreased respectively to 9.9 dB (±2.5) and 6.5 dB (±3.9) at 1 month and to 8.52 dB (±2.8) and 5.2 dB (±3.9) at 6 month and to 11.5 dB (±0.7) and 4.5 dB (±3.5) at 12 months and to 8.2 dB (±5.3) and to 4.4 dB (±4.2) at 18 months (Fig. 2).

Microperimetry

In the CRVO and BRVO groups, the mean MP values were respectively 127.3 (±21.9) and 197.3 (±97.0) at presentation and increased to 241 (±88.2) and 311.9 (±101.2) at 12 months. At 18 months the values increased to 237 (±35.5) in the CRVO group, and to 328.2 (±93.7) in the BRVO group (Fig. 3).

OCT

The OCT at presentation demonstrated the presence of macular edema in both groups (704.66 ± 204.51 µm

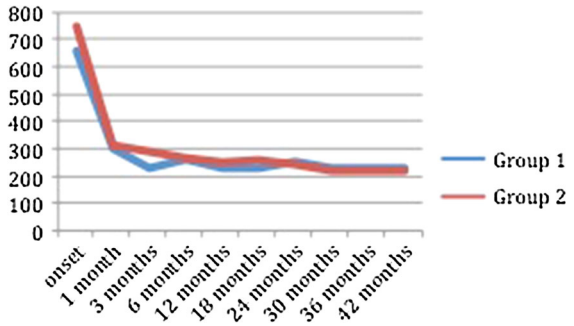

Fig. 4 Graph of OCT thickness in the 2 groups from *onset* to 42 months of follow-up

in the CRVO and 654.53 ± 179.52 μm in the BRVO group). The edema was clearly cystic with fluid entrapped in the external plexiform layer and in the inner nuclear layer along with RPE detachment in the fovea. The thickness of the central retina decreased significantly ($p < 0.01$) at follow-up visits (respectively to 246 ± 45.45 μm at 12 months and 220.52 ± 63.23 μm at 18 months in the CRVO group and 240.85 ± 50.45 μm at 12 months and 255.37 ± 92.54 μm at 18 months in the BRVO group) (Fig. 4).

Fluorescein angiography

FA performed between 12 and 18 months evidenced the presence of retinal neovessels in the context of ischemic areas in 8 out of 44 patients.

Summary of outcomes

All graphs show not only an improvement but also a stabilization in the parameters evaluated during follow-up and the improvement in the parameters between onset and follow-up visit at 42 months was shown to be statistically significant by the *t* test ($p > 0.001$ for visual acuity, macular thickness, MP values, and MD of visual field data at presentation and at last follow-up visit in both groups). It is interesting to note that evolution of all parameters were equally positive independently from the number of injections, the only difference among groups being the number of injections to achieve the same positive results.

MD in VF re-increased over time in group 2 which could be explained by the damaging effect of recurrent edema outside the macula between injections.

This was not the case of MP values that remained high after 42 month of follow-up, indicating favorable evolution of the central macula.

Laser flare photometry

Mean laser flare photometry values were 9.9 ± 2.9 ph/ms before injection, 8.8 ± 3.3 ph/ms after 4 injections, and 7.3 ± 2.7 at last follow-up with no statistical significant difference ($p > 0.05$), showing that bevacizumab injection had no deteriorating effect on blood ocular barrier.

Number of injections & failures

Analyzing the long-term management, using the cut-off of 4 injections, 31 eyes received 1–4 injections (mean 2.59 ± 1.10) and 13 eyes received more than 4 injections (mean 10.83 ± 6.18). In the first group, all eyes showed resolution of the edema with no recurrence during a minimum follow-up period of 1 year (mean follow-up). In the group needing sustained injections only one patient showed resolution after 10 injections, all other patients needed ongoing sustained injections until the present time of follow-up. Four patients were failures with persistence of a significant edema. Of these patients, one had completely uncontrolled diabetes and developed an anterior non arteritic ischemic neuropathy and one patient refused to pursue injections after the fifth injection despite good response.

Injection time interval

A regular time interval could be determined for 8/13 eyes with a standard deviation of less than 1.7. Injection intervals were respectively 5 ± 1.4 weeks, 5.1 ± 0.66, 6.16 ± 1.6, 6.45 ± 1.3, 10.6 ± 1.6, 14.0 ± 1.4, 14.4 ± 1.2, and 17.3 ± 1.7. In one patient, time interval between injections was more variable with intervals of 19.1 ± 4.4 weeks when considering the whole period. The mean time for re-injection in the sustained injection group was 11.2 ± 2.6 weeks, an information not very useful in order to determine injection interval and injection pattern for each individual case to minimize follow-up visits.

Disease complications

At 18 months, 8/44 eyes (18.2 %) had significant ischemic areas and/or retinal neovessels. Two patients belonged to group 1 and 6 patients to group 2. Seven patients were treated by peripheral laser treatment (PLT) with favorable evolution and one patient, although scheduled for PLT, presented vitreous bleeding needing vitrectomy with a favorable evolution.

Procedure complications

No significant side effects or local and/or systemic complications were recorded in relation with the injection.

Discussion

Macular edema due to BRVO or CRVO has been associated with deleterious consequences on visual acuity [5, 6].

The standard therapy consisted mainly of grid laser or scatter laser retinal coagulation associated with some improvement on visual outcome [23–25], long-term visual gain being however of limited importance [26–28].

Soon after the start of 21st century, the tremendous efficacy of anti-VEGF agents for macular edema caused by BRVO and CRVO was noticed and became evident without a clear explanation being available for such a potent effect in this situation [20, 29].

The availability of a pharmacologic principle of such potency combined with so little side effects is a rare occurrence in medicine. The high therapeutic index obtained by anti-VEGF agents for BRVO/CRVO related macular edema made it hard to justify prospective double masked randomized trials [30]. The disadvantage was however that in a large proportion of cases the effect of anti-VEGF therapy is of limited duration and has to be repeated which we proved in this work [31, 32].

The question hence was not whether anti-VEGF agents should be used but how they should be used. Therefore, it was important to perform observational longitudinal studies [32, 33].

We present here the results of a study conducted over 7 years on the modalities of anti-VEGF management of BRVO/CRVO associated macular edema. The response rate to anti-VEGF therapy (bevacizumab) was extremely high as only 4/44 eyes (9 %) did not respond to treatment. Visual outcome was also extremely good and much better than historical series treated with laser in both CRVO and BRVO cases with a respective improvement from 0.15 to 0.66 for the CRVO group and from 0.26 to 0.92 for the BRVO group.

The proportion of cases needing 4 injections or less (mean of 2.59 injections) was 70 %, all of which could be considered stabilized (no recurrence after 9 months of follow-up). Thirteen patients (29.5 %) needed more than 4 injections (mean 10.83) allowing them to maintain the regained visual acuity. In this group, only one patient was considered stabilized after 10 injections. Two other functional parameters were useful and complementary for monitoring evolution, computerized VFT and MP. Evolution in visual fields was less favorable in the sustained injection group reflecting extra-macular damage (edema). However, MP improved in parallel with VA in both groups and was found to be more reliable to monitor macular function. Mean macular thickness improved similarly in both the "low-injection group" and in the sustained injection group with a mean reduction of 399.7 and 529.6 μm, respectively.

One important problem beyond efficacy of treatment is the burden to the patient of repeated injections. Patients tend to become weary of repeated office visits and decide to abandon care. This was the case for the 7 patients where data and follow-up was insufficient. Most of these patients were seen at the start of this new procedure when the need for repeated injections was not yet known. Therefore, patient should be warned that repeated injections will probably be necessary and it should be attempted to reduce office visit to a minimum. In this perspective, we tried to determine individual time intervals of recurrence that we were able to establish in 8/9 evaluable eyes in sustained injection group (excluding the four eyes that were failures). This allowed us to offer customized care, reducing office visits by scheduling check-ups around the time interval of expected recurrence. Determination of such an individual time interval is presently searched in many centers for RVO and AMD and seems to be possible in a large proportion of cases as our results show in this longitudinal follow-up profile [38, 39].

This study also made us realize that the distinction of ischemic from non-ischemic RVO is losing its

importance. Indeed during sustained injections, the danger of ischemic complications is minimized due to the anti-angiogenic effect of anti-VEGF treatment. Ischemic complications needing laser therapy occurred in 8/44 (18.1 %) patients. All these patients were detected by angiography performed after 18 months after entry or 12 months after the last injection of bevacizumab. Although the risk for neovessels is lower because of anti-VEGF therapy, angiographic control should not be neglected, especially in those cases where injections could be stopped. However, thanks to anti-VEGF therapy laser as a primary treatment, aimed at reducing edema can be avoided allowing a better retinal function.

The quasi complete lack of side effects and complications of this treatment in accordance with safety results of anti-VEGF agents in AMD [33] reduces the use of intraocular steroids to a minimum which should be reserved to those cases failing to respond to anti-VEGF treatment estimated to be less than 10 % in our hands. Intraocular steroids do also need to be re-injected and the risk for side effects including ocular hypertension, cataract, and infection is cumulative [34, 35].

In our opinion intraocular steroids should never be used as a primary treatment option, as side effects are much higher whereas the duration of the effect is comparable to anti-VEGF treatment [36, 37].

All functional parameters (VA, VFT, and MP) always lagged behind morphological parameters such as OCT, worsening after thickening was seen on OCT and improving after thinning was seen on OCT.

In summary, this longitudinal study conducted over 6 years shows that intraocular anti-VEGF therapy represents a major impact on the management of RVO.

Thanks to the tremendously high therapeutical index, it has become the undisputed first-line therapy rendering grid laser obsolete and reducing the need for alternative intraocular corticosteroids to less than 10 %.

It transformed CRVO from a blinding disorder into a condition where a vision of 0.5 can be expected on the average and allows a visual outcome of 0.8 for BRVO.

The problem that somewhat tempers these good results is the recurrence of macular edema needing repeated injections in a little over 1/3 of cases. Precise functional and morphological follow-up modalities such as MP and OCT allow to determine in a large proportion of cases a recurrence pattern that allows to reduce to a minimum office visits in these patients.

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