
Perspective in Ophthalmology

Combination therapy in diabetic macular oedema and retinal vein occlusion – past and present

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ABSTRACT.

This paper summarizes the recent evidence for combined therapies in the intravitreal medical treatment of diabetic macular oedema or macular oedema, secondary to retinal vein occlusion. Since the introduction of anti-inflammatory or anti-VEGF drugs combined with or used alternatively to laser, visual acuity can be stabilized or improved in a significant number of patients. However, there is an ongoing debate regarding the safety, efficiency and economic concerns related to these intravitreal monotherapies because they warrant frequent repetition to maintain the clinical effect. In the literature, the combination of photolasercoagulation, intravitreal steroids or VEGF-inhibitors, or both, shows early compelling evidence that some patients may benefit from less retreatment compared to monotherapy. To provide a conceptual and perspective approach for a first-line combined therapy, this paper also summarizes own results of pilot interventional case series of a 1.5 cc core pars plana vitrectomy and intravitreal substitution with balanced salt solution (BSS), 1.25 mg bevacizumab and 8 mg triamcinolone.

Keywords: bevacizumab – combination therapy – core vitrectomy – diabetic retinopathy – macular oedema – pharmacosurgery – retinal vein occlusion – triamcinolone

Acta Ophthalmol.

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doi: 10.1111/j.1755-3768.2010.01962.x

Introduction

Diabetic retinopathy (DR) and retinal vein occlusion (RVO) are the two major retinal vascular diseases worldwide in people aged 20–74 years (DR) and over 65 years (RVO) (Moss et al. 1998; Ryan 2006). Macular oedema is the principle cause of visual loss and blindness (Stefansson et al. 2000). In

both entities, acute and chronic macular oedema can be classified based on their morphology into focal and diffuse oedema types; moreover, ischaemic and nonischaemic forms of macular oedema can be differentiated by fluorescein angiography (FA) assessing parameters like enlarged foveal avascular zone (FAZ) or capillary dropout in the macula. Our primary goal was to

present a literature review on the evolution from mono- to combination therapy in DME and RVO, while our secondary goal was to present one innovative combination therapy regimen for these two diseases.

DME

Ferris and Patz observed that 53% of 135 eyes with diabetic macular oedema (DME) lost two or more lines of visual acuity over a 2-year period (Ferris & Patz 1984). In the Early Treatment Diabetic Retinopathy Study (ETDRS), 33% of 221 untreated eyes available for follow-up at the 3-year visit, all with oedema involving the fovea at baseline, had experienced a 15- or more letter decrease in visual acuity, defined as 'moderate visual loss' (equivalent to a doubling of the visual angle; 20/25–20/50; ETDRS report 4, 1987).

Monotherapy

Focal/grid photocoagulation of eyes with clinically significant macular oedema (CSME) reduced the risk of moderate visual loss from 24% to 12% in all types of oedema 3 years after the initiation of treatment but spanning from 17% to 8% for those without foveal involvement to 35–17% for those with foveal involvement (ETDRS report 1, 1985). However, it is recognized that changes in high contrast central visual quality represent only a

poor and extremely limited understanding of the induced vision changes, and recommendations have been made to include contrast target discrimination not only at fixation but throughout the central visual field to better understand the functional impact of the chorioretinal scars that are produced and that expand with time (Sinclair et al. 1999; Meyer 2007).

The microvascular pathology produced by diabetic microangiopathy (capillary basement membrane thickening, pericyte loss, microvascular occlusion and leakage with microaneurysm formation) result in years of abnormal leakage of serum macromolecules, into the extravascular space followed by an oncotic influx of water resulting in the macular oedema (Ciulla et al. 2003; Ryan 2006). Increased serum extravasation from the choriocapillaris through the retinal pigment epithelium (RPE) into the retina is also thought to contribute to DME (Antcliff & Marshall 1999). Pharmaceutical treatment has consisted predominantly of anti-VEGF compounds and steroids because of their properties to increase tight-junction proteins and local vasoconstriction (anti-oedematous), decrease inflammation and their ability to reduce vascular leakage (angiostatic).

Compared with modified focal/grid photocoagulation, single intravitreal one or four mg triamcinolone demonstrated no benefit on visual acuity development in DME over 3 years (Beck et al. 2009 for the DRRC network). The DRRC net used ETDRS high-contrast acuity only, thereby missing low-contrast vision problems, which are by far the greatest complaints of patients with DME, that have been demonstrated after focal lasercoagulation (Sinclair et al. 1999). On the other hand has been demonstrated that the repetitious 4 mg triamcinolone injection can significantly reduce refractory diabetic macular oedema (Gillies et al. 2006; Jonas 2006) as does a sustained-release fluocinolone acetonide intravitreal implant (Elliot 2009). There have not been any clinical trial to select the optimal dosage or to calculate retreatment intervals, and the incidence of side-effects such as cataract induction or increase in intraocular pressure (IOP) are unsolved up to date (Krepler et al. 2005; Audren et al. 2006).

The increase in retinal capillary and RPE permeability is mediated in part by vascular endothelial growth factor (VEGF), which is upregulated in secondary to the hypoxia accompanying the microangiopathy (Shima et al. 1995; Dvorak et al. 1999; Noma et al. 2006; Kern 2007). Recently, agents that suppress VEGF, such as the selective VEGF-165 isoform blocker pegaptanib sodium (Macugen[®]; Eyetech Inc, Cedar Knolls, NJ, USA), or the two recombinant pan VEGF-A blocker ranibizumab (Lucentis[®]; Genentech, San Francisco, CA, USA) and bevacizumab (Avastin[®]; Genentech), have been evaluated in the management of macular oedema because of DR (Cunningham et al. 2005; Avery et al. 2006). However, there is concern because of the requirement for ongoing monthly or 6 weekly injections (Pruente 2009) and the extended dosing schedules, which are under investigation. There is a poor knowledge and concern at this time about the effect of reaccumulation of the oedema and how the anti-VEGF therapy should then be discontinued (Matsumoto et al. 2007) or if progressive macular ischaemia may diminish the efficacy of anti-VEGF (Chung et al. 2008). Furthermore, as VEGF naturally serves as a survival factor for existing vessels and neuronal cells, prolonged VEGF blockade thus might impair VEGF-mediated normal vascular and RPE repair (Oosthuysen et al. 2001; Jin et al. 2002; Gillies 2006).

Combination therapy

Incorporating the two pharmacological strategies (corticosteroids and anti-VEGF agent), up to date three prospective, controlled studies had been conducted to examine the effects of combined therapy of intravitreal bevacizumab and triamcinolone for DME ranging from four (Faghihi et al. 2008) to 6 months (Ahmadiéh et al. 2008) and to 9 months (Soheilian et al. 2009). Within two of these studies (Faghihi et al. 2008; Soheilian et al. 2009), the combination arm was identical with an initial and one time application of 1.25 mg bevacizumab and 2 mg triamcinolone at a volume of 0.1 ml, which was not combined with a vitrectomy or a paracentesis. Ahmadiéh et al. added two booster bevacizumab injections in 6-week intervals and demonstrated

with Faghihi et al. (2008) that their combination therapies induced earlier visual acuity improvement than bevacizumab monotherapy. Soheilian et al. (2009) could not confirm a better visual outcome of the combination therapy group and conclude no adjunctive effect of 2 mg triamcinolone; however, the retreatment rate during the follow-up period was smaller than in the bevacizumab monotherapy group.

RVO

Retinal vein occlusion is the second most common and important retinal vascular disease after diabetic retinopathy. In most patients, the haemorrhage, oedema and microvascular ischaemia of RVO are caused by the obstruction of venous flow, with elevated intra-capillary hydrostatic pressure and microvascular occlusion with leucocytes that occur in the distribution of the affected vessel, a central (CRVO) or branch retinal vein (BRVO – The Eye Disease Case-Control Study Group 1993, 1996; Shahid et al. 2006). With time, the extent of retinal haemorrhage and oedema may decrease or resolve completely with the development of collaterals and with some capillary recanalization. Macular oedema often persists despite resolution of the retinal haemorrhages and may result in RPE atrophy (Ryan 2006).

Monotherapy

The branch retinal vein and central RVO studies were designed to evaluate whether argon laser photocoagulation could improve macular oedema that had decreased visual acuity to 20/40 or worse. It was demonstrated that 65% improved two or more lines after laser versus 37% of eyes with observation (The Branch Vein Occlusion Study Group 1984). In CRVO, however, grid laser demonstrated no superior efficacy in visual acuity to observation CRVO (The Central Vein Occlusion Study Group 1995).

Treatment with intravitreal corticosteroids such as triamcinolone acetonide or dexamethasone was shown to reduce macular oedema in several studies (Greenberg et al. 2002; Park et al. 2003; Cekić et al. 2005; Jonas 2006; Sivaprasad et al. 2006), through a multicomponent mechanism (Kuppermann et al. 2007). In two prospective, multi-

centre, randomized clinical trials, 1 or 4 mg of intravitreal triamcinolone was evaluated compared with the natural course (CRVO study) or grid laser-photocoagulation (BRVO study). In the CRVO trial, intravitreal triamcinolone injections over 2 years resulted in an improved superiority over observation with the 1-mg dose, which had a safety profile superior to that of the 4-mg dose (Ip et al. 2009). In the BRVO trial on the contrary, there was no difference identified in visual acuity at 12 months for the standard care group (grid) compared with the triamcinolone groups (Domalpally et al. 2009).

Intravitreal injections of bevacizumab have been demonstrated to significantly reduce macular oedema and to improve visual acuity by up to three lines in 73% of 18 CRVO and in 77% of 22 BRVO patients (Schaal et al. 2007; Stahl et al. 2007). The maximum reduction in the macular oedema is usually observed within the first 4 weeks of treatment. Because the macular oedema often relapses after discontinuation of treatment, repeated injections were required in most patients. Spaide et al. in eyes with CRVO demonstrated an 18-letter increase with repeated intravitreal ranibizumab injections over the period of 1 year averaging 8.5 injections (Spaide et al. 2009). However, no observations or comments have been forthcoming about whether the injections are required beyond the 1-year development of collaterals to prevent the recurrence of the oedema.

DME and RVO – vitrectomy

The human vitreous gel undergoes progressive liquefaction with age, but in diabetic retinopathy, the consistency of the collagen fibrils is more dense (Faulborn et al. 1998). The importance of the vitreous in the progression of diabetic retinopathy may also extend beyond tractional considerations, as it is believed that the vitreous serves as scaffolding for new vessel formation and may also contribute to the molecular imbalances that lead to diabetic retinopathy progression. Stefansson et al. suggested that both panretinal photocoagulation (PRP) and vitrectomy reduce diabetic macular oedema and retinal neovascularization by increasing the oxygen redistribution in favour of the posterior pole (Stefansson et al.

1981; Stefansson & Landers 2006). This has also been advocated in RVO that macular oedema resolved after vitrectomy and separation of the posterior hyaloid with or without additional gas tamponade (Kurimoto et al. 1999). In addition, if ILM is peeled with the vitrectomy, some have suggested that macromolecules, such as serum lipoproteins and growth factors such as VEGF and others, may gain diffusion release, while others have demonstrated that there is improved oxygenation at the surface of the retina with the removal of preretinal gel that may result in reduced production of the hypoxia-derived factors (personal communication with NM Holekamp at the 12th Vitreo-Retinal Symposium, 28–29th of August 2009 Frankfurt am Main, Germany <http://www.vrs-online.com> based on the paper by her and co-workers [Shui et al. 2009]). Pars plana vitrectomy therefore appears to offer a long-term potential treatment for macular oedema but might require ILM and/or ERM removal to gain maximal theoretical effect. The long-term effects of mechanical injury of a ILM peeling depends moreover on the variety of competent surgical skills, and ILM staining long-term effects are still unknown. Therefore, whether simple core vitrectomy, with immediate or induced ‘over-the-time’ release of the posterior hyaloids perhaps combined with PRP, but without peeling of the ILM, is sufficient to reduce macular oedema and improve vision outcomes, remains debated.

Combination treatment – intrectomy

As noted earlier, monotherapy with focal laser appears to reduce oedema but without VA improvement. Oedema very likely recur because of leakage of other areas of progressive ischaemia, and repeated laser treatments may further compromise paraxial vision because of accumulated scars that expand over time (Sinclair et al. 1999). Pharmaceutical monotherapy appears to improve vision in a substantial portion of patients but is problematic by requiring unceasing reinjections and with accumulating side-effects as has been demonstrated with steroids or implicated with long-term repeated anti-VEGF agents. Pars plana vitrectomy appears to offer a prolonged solution, but whether it must be per-

formed with the removal of ERM/ILM and the resultant mechanical injury are unknown and whether comparative sufficient prolonged effect may be gained by a simple vitrectomy with posterior hyaloids separation is also unknown. Therefore, it appears that a combined solution would be most opportune, where the simplification of the surgery such that it can be performed in an outpatient setting, either Ambulatory Surgical Centre or potentially office, would reduce the costs and morbidity significantly, which has been demonstrated in AMD treatment previously in a similar combination therapy regimen (Koss et al. 2009).

To evaluate this concept, a pilot study was performed to evaluate the effects of combining a posterior core pars plana vitrectomy (cppV) as mentioned earlier with a simultaneous intravitreal drug treatment using triamcinolone (because of its long-lasting anti-oedematous properties) and bevacizumab (because of its long-lasting anti-angiogenic properties) for a multifactorial therapy of diabetic macular oedema and macular oedema secondary to CRVO and BRVO. The study was performed to gain information in a selected series of patients for calculating patient requirement numbers for a planned multicentre, prospective, randomized study of the effects of such combination pharmacocurgery on macular oedema in DR and RVO eyes in the future.

Methods

All eye surgeries were performed using a standard protocol at the Department of Vitreo-Retinal Surgery/Ophthalmology of the Goethe-University in Frankfurt/Main, Germany. Every patient received antibiotic eye drops 4 times per day during the 3 days preceding the surgery (gentamicin, Refobacin[®], Merck, Darmstadt, Germany). In the operating room, lid and skin irrigation with 10% povidone iodine solution was performed for 5 min, and 5% povidone iodine conjunctival drops were administered for 3 min in an antiseptic setting (antiseptic surgical gloves and drape, closed lid retractor).

A cppV was carried out using a vitrector (Fig. 1; Intrector[®], Insight Instruments, Stuart, FL, USA), which has an integrated cutter up to 699 cuts/min and combines two separate channels

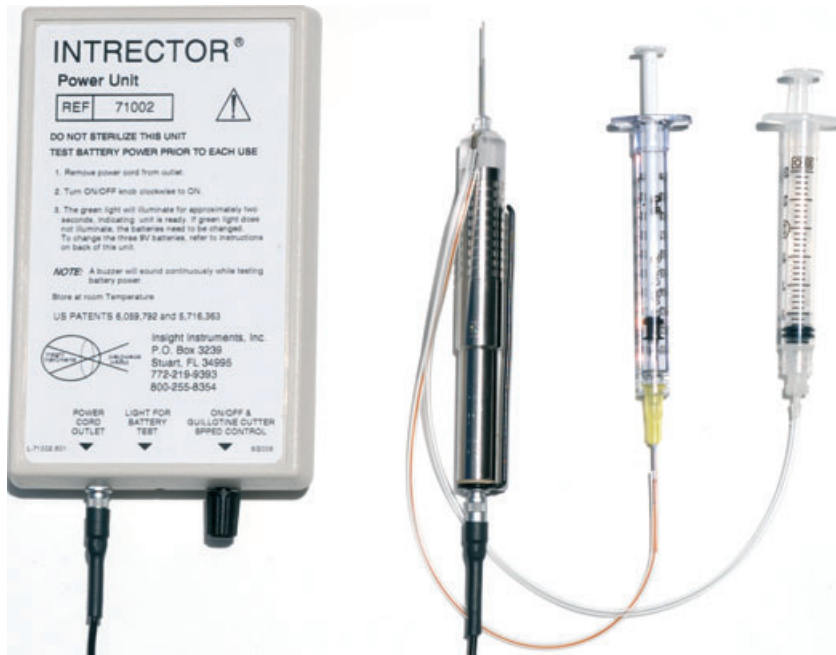


Fig. 1. Intrector® unit currently battery driven.

for aspiration and infusion within a single 23 gauge probe tip. In total, 1.5 ml of cut vitreous was aspirated guided by indirect funduscopy with the following goals/endpoints of the

- (1) cut visible vitreous bands and
- (2) cause vitreous liquefaction and induce subsequent posterior vitreous detachment (PVD)
- (3) leave the anterior part of vitreous posterior to the lens
- (4) and deliver the two drugs, separately in two syringes, safely to the posterior pole without rising the perioperative IOP.

The solution used for injection contained 1.2 ml of balanced salt solution, 8 mg (0.2 ml) preservative-free triamcinolone acetonide (Volon A®, Dermapharm, Grünwald, Germany) and 1.25 mg (0.1 ml) bevacizumab (provided by the compound pharmacy of the University Hospital at the Johann Wolfgang Goethe-University in Frankfurt/Main, Germany). All patients were followed at 24 hr postoperatively to check for anterior chamber and vitreous reaction and monitoring of the IOP.

Patients

Study design and patients

The data of this interventional pilot case series of patients with a deterior-

ation of vision caused by macular oedema secondary to DR (60 patients with $n = 73$ eyes; mean age: 65.2 years) or RVO (47 patients with $n = 47$ eyes; mean age: 66.6 years) was retrospectively analysed. All of the patients had cystic diffuse macular oedema within one disc diameter of centre and were not treated before (primary ME). None of the eyes had a history of glaucoma, chronic or acute intraocular inflammation, macular degeneration or dystrophy, prior pars plana vitrectomy, or a poor vision related to cataract, or prior central (GRID or modified GRID) laser photocoagulation. Informed consent was obtained from each patient before treatment in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The probability of a spontaneous resolution of the macular oedema, the risks and benefits of the proposed treatment, and the off-label use of bevacizumab were explained.

Measurements

At baseline and at all scheduled follow-up visits, an ophthalmic examination (slit lamp biomicroscopy and indirect ophthalmoscopy) was performed, and the best-corrected visual acuity (BCVA) was determined using Snellen charts with the false choice tech-

nique with a minimum of four of five optotypes. Best-corrected visual acuity values were transformed to the logarithm of the minimum angle of resolution (LogMAR). The IOP was measured using Goldmann applanation tonometry, and the central foveal thickness was assessed by optical coherence tomography (line and retinal thickness map mode; Model 3000 Stratus OCT®, Carl Zeiss Meditec, Jena, Germany). The same protocol was repeated at each follow-up visit. Fluorescein angiography was carried out prior to the day of surgery and at the last follow-up visit (or at T1 and T2 if appropriate). In addition, the need for retreatment (with intravitreal combination therapy) was recorded, and adverse events were monitored throughout the study.

Data analysis

For statistical analysis, the EXCEL® (Microsoft, Redmond, WA, USA) and BiAS® software (Version 8.2 for WINDOWS®, Epsilon-Verlag, Darmstadt, Germany) were used. The David's test was performed to identify parametrical distribution, and the data set were declared as nonparametrical. Therefore, the Wilcoxon matched pairs and Friedman test were performed to evaluate the change in BCVA and central retinal thickness from baseline to each follow-up visit within each group.

Interventions

Patients were considered for retreatment using the intravitreal combination therapy, if the macular oedema persisted for 4 months after the initial pharmacosurgery or if there was a decrease in BCVA of ≥ 1 Snellen lines because of a relapse of macular oedema (increase by 150 μm) detected by ophthalmic examination, optical coherence tomography or FA.

Panretinal or focal laser photocoagulation were applied after the initial treatment depending on the results of the FA weighing the presence of neovascularizations elsewhere, at the disc or central persisting microaneurysma leakage in FA comparing baseline to results at the termination of the follow up period (DME 6 months and RVO 36 weeks).

Results

DME

Three groups of patients were formed by FA and followed for a minimum of 6 months: eyes with nonproliferative diabetic retinopathy (NPDR) without ischaemic maculopathy ($n = 38$), eyes with NPDR with ischaemic maculopathy ($n = 17$), and eyes with proliferative diabetic retinopathy (PDR) with or without ischaemic maculopathy ($n = 18$). The three groups were overall similar with regard to the demographic and baseline characteristics. Because of the retrospective evaluation, the degree of a posterior vitreous detachment was assessed on OCT scans. Thus, we observed posterior vitreous detachments in approximately 30% of the patients. Mean BCVA at baseline was higher in eyes with NPDR without ischaemic maculopathy (0.52) than in eyes with NPDR

with ischaemic maculopathy (0.99) and intermediate in eyes with PDR (0.77) (Table 1).

A statistically significant increase in mean BCVA was observed in all 73 eyes with DR at 2 months after the initial operation ($p < 0.05$ versus baseline). Thereafter, different trends were noted for the three patient groups. In eyes with NPDR without ischaemic maculopathy, the increase in BCVA remained stable from the 2nd follow-up examination at 4 months, with a statistically significant difference in mean BCVA at 6 months (-0.16 logMar, $p < 0.01$ versus baseline). By contrast, in eyes with NPDR with ischaemic maculopathy and in eyes with PDR, BCVA values at 4 and 6 months after the initial surgery were lower than at 2 months.

Overall, in 43 of 66 eyes with DR (65.2%), a statistically significant improvement in mean BCVA (-0.14

logMar versus baseline) was observed at the end of the follow-up period, i.e. at 6 months after initial treatment ($p < 0.01$ versus baseline). In 11 eyes (16.7%), BCVA remained stable, and in 12 eyes (18.2%), a deterioration of BCVA was noted.

Over the 6-month observation period, retreatment with the intravitreal combination therapy was performed in 20 of 73 eyes (27.4%, Fig. 2). The retreatment rate was higher for eyes with NPDR without ischaemic maculopathy (14/38; 36.8%) than for eyes with NPDR with ischaemic maculopathy (5/17; 29.4%) and was lowest for eyes with PDR (1/18; 5.6%) (Fig. 2). Interestingly, laser photocoagulation was only carried out in more than half of the eyes with PDR (10/18; 55.6%), in about one-third of the eyes with NPDR with ischaemic maculopathy (6/17; 35.2%) and in about one-fifth of the eyes with NPDR (8/38; 21.0%).

Table 1. Best-corrected visual acuity (BCVA) in eyes with nonproliferative diabetic retinopathy (NPDR) with ischaemic maculopathy (IM), NPDR without IM and proliferative diabetic retinopathy (PDR) before (T0) and after treatment (T1-3). Significance was tested using the Friedman test for nonparametrically distributed data; significant p-values are highlighted in bold.

Group (no. of eyes)	BCVA in mean values \pm standard deviation; Median values with value range (r) and 95% Confidence interval (CI); All values in LogMar			
	Baseline (T0)	2 months (T1)	4 months (T2)	6 months (T3)
NPDR and IM ($n = 17$)	Mean 0.99 ± 0.5 Median 1.00 (range/ r 0.4–2.19; 95% confidence interval/CI 0.52–1.3)	0.64 ± 0.18 0.69 (r 0.3–1.0; CI 0.52–0.69)	0.77 ± 0.43 0.69 (r 0.3–2.0; CI 0.39–1.0)	0.82 ± 0.41 0.69 (r 0.3–2.1; CI 0.52–1.0)
		T1 versus T0: $p < 0.05$	T2 versus T0: $p = 0.22$ T2 versus T1: $p = 0.34$	T3 versus T0: $p = 0.36$ T3 versus T1: $p = 0.22$ T3 versus T2: $p = 0.28$
NPDR without IM ($n = 38$)	0.52 ± 0.21 0.52 (r 0.15–1.0; CI 0.39–0.69)	0.44 ± 0.21 0.39 (r 0.10–1.00; CI 0.30–0.52) T1 versus T0: $p = 0.68$	0.36 ± 0.16 0.39 (r 0.10–0.7; CI 0.30–0.39) T2 versus T0: $p < 0.01$ T2 versus T1: $p < 0.05$	0.36 ± 0.16 0.39 (r 0.1–0.7; CI 0.30–0.39) T3 versus T0: $p < 0.01$ T3 versus T1: $p < 0.05$ T3 versus T2: $p = 1$
PDR ($n = 18$)	0.77 ± 0.42 0.69 (r 0.3–1.89; CI 0.39–1.0)	0.53 ± 0.24 0.52 (r 0.15–1.0; CI 0.30–0.69) T1 versus T0: $p = 0.22$	0.62 ± 0.29 0.69 (r 0.15–1.0; CI 0.39–1.0) T2 versus T0: $p = 0.41$ T2 versus T1: $p = 0.67$	0.72 ± 0.34 0.69 (r 0.15–1.30; CI 0.52–1.0) T3 versus T0: $p = 0.91$ T3 versus T1: $p = 0.35$ T3 versus T2: $p = 0.72$
All (mean) ($n = 73$)	0.69 ± 0.4 0.52 (r 0.15–2.1; CI 0.52–0.69)	0.51 ± 0.22 0.52 (r 0.10–1.0; CI 0.49–0.52) T1 versus T0: $p < 0.05$	0.52 ± 0.33 0.39 (r 0.1–2.0; CI 0.39–0.52) T2 versus T0: $p < 0.01$ T2 versus T1: $p = 0.55$	0.55 ± 0.34 0.52 (r 0.10–2.1; CI 0.39–0.52) T3 versus T0: $p < 0.01$ T3 versus T1: $p = 0.73$ T3 versus T2: $p = 0.99$

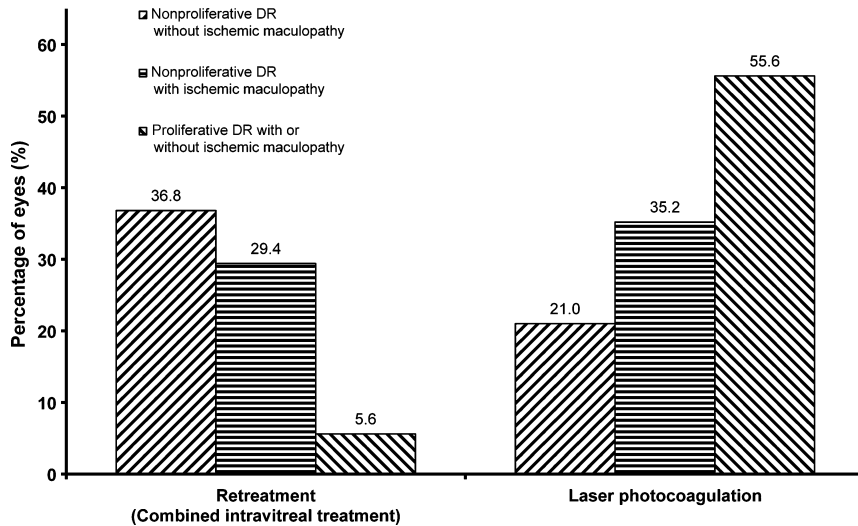


Fig. 2. Proportion of eyes with diabetic retinopathy receiving further treatment at the end of the follow-up period at T3.

RVO

Based on the results of the FA, three groups of patients were defined and followed for 36 weeks: eyes with ischaemic CRVO defining ischaemia

as having greater than 10 disc areas of capillary nonperfusion ($n = 15$), eyes with nonischaemic CRVO ($n = 7$) and eyes with BRVO ($n = 25$). Before the initial examination at our institution, the patients had noticed

deterioration in vision, which lasted 24 ± 16 days (mean \pm SD). Based on the onset of the deterioration defined by history, there were 25.5 ± 20 weeks (mean \pm SD) for the macular oedema to resolve spontaneously. Thus, all patients were classified to have persistent, nonresolving macular oedema.

In all eyes ($n = 47$), a statistically significant increase in BCVA was observed at 36 weeks after the initial operation (T3) ($p < 0.01$ versus baseline, Table 2). The difference in BCVA versus baseline was already statistically significant at 13 weeks (T1) for eyes with BRVO ($p < 0.01$), at 23 weeks (T2) for eyes with ischaemic CRVO ($p < 0.05$) and at 36 weeks (T3) for eyes with nonischaemic CRVO ($p < 0.01$). The change of BCVA, expressed in LogMar, was on a higher scale in eyes with nonischaemic CRVO and BRVO (0.37 and 0.44 LogMar after 36 weeks) than in eyes with ischaemic CRVO (1.02 LogMar). The relative decrease, however, was larger in eyes with ischaemic CRVO (-65%) than in

Table 2. Best-corrected visual acuity in eyes with central (CRVO) or branch retinal vein occlusion (BRVO) before (T0) and after treatment (T1-3) Significance was tested using the Friedman test for nonparametrically distributed data; significant p-values are highlighted in bold.

Group (no. of eyes)	BCVA in mean values \pm standard deviation; Median values with value range (r) and 95% Confidence interval (CI); All values in LogMar			
	Baseline (T0)	13 weeks after treatment (T1)	23 weeks after treatment (T2)	36 weeks after treatment (T3)
Ischemic CRVO ($n = 15$)	1.86 \pm 0.54 2.00 (r 1.00–2.69; CI 1.30–2.22)	1.71 \pm 0.62 2.00 (r 0.52–2.39; CI 1.00–2.22) T1 versus T0: $p = 0.12$	1.44 \pm 0.57 1.30 (r 0.39–2.22; CI 1.00–2.1)	1.31 \pm 0.59 1.00 (r 0.52–2.09; CI 1.00–2.00)
			T2 versus T0: $p < 0.05$ T2 versus T1: $p = 0.24$	T3 versus T0: $p < 0.01$ T3 versus T1: $p < 0.05$ T3 versus T2: $p < 0.05$
Non-ischemic CRVO ($n = 7$)	0.80 \pm 0.19 0.69 (r 0.52–1.0; CI 0.52–1.0)	0.64 \pm 0.37 0.52 (r 0.30–1.30; CI 0.30–1.30) T1 versus T0: $p = 0.21$	0.51 \pm 0.29 0.39 (r 0.16–1.0; CI 0.16–1.00)	0.43 \pm 0.33 0.30 (r 0.05–1.0; CI 0.05–1.00)
			T2 versus T0: $p = 0.06$ T2 versus T1: $p = 0.16$	T3 versus T0: $p < 0.05$ T3 versus T1: $p = 0.07$ T3 versus T2: $p = 0.13$
BRVO ($n = 25$)	0.77 \pm 0.39 0.69 (r 0.16–1.52; CI 0.52–1.00)	0.49 \pm 0.33 0.39 (r 0.00–1.30; CI 0.30–0.69) T1 versus T0: $p < 0.01$	0.40 \pm 0.38 0.39 (r 0.0–1.3; CI 0.22–0.49) T2 versus T0: $p < 0.01$ T2 versus T1: $p = 0.07$	0.33 \pm 0.24 0.30 (r 0.0–1.00; CI 0.16–0.39) T3 versus T0: $p < 0.01$ T3 versus T1: $p < 0.05$ T3 versus T2: $p = 0.06$
All (mean) ($n = 47$)	1.12 \pm 0.66 1.00 (r 0.16–2.69; CI 0.69–1.30)	0.90 \pm 0.71 0.69 (r 0.00–2.39; CI 0.39–1.0) T1 versus T0: $p < 0.05$	0.75 \pm 0.65 0.52 (r 0.0–2.22; CI 0.39–1.0) T2 versus T0: $p < 0.01$ T2 versus T1: $p = 0.11$	0.66 \pm 0.59 0.52 (r 0.00–2.09; CI 0.30–0.60) T3 versus T0: $p < 0.01$ T3 versus T1: $p < 0.01$ T3 versus T2: $p = 0.21$

eyes with nonischaemic CRVO (-54%) and eyes with BRVO (-43%).

The combined intravitreal regimen had to be repeated after 36 weeks because of a relapse in macular oedema and a decrease in VA regarding the intervention criteria in 51% (24/47) of all eyes. The relative retreatment rate was 100% (7/7) in the nonischaemic CRVO and 75% (10/15) in the ischaemic CRVO group, whereas it was relatively low with 36% (9/25) in the BRVO group.

In patients with ischaemic CRVO, PRP was carried out (beginning after 36 weeks after T0) in 7/15 eyes (47%) and in 1/25 BRVO eye (4%) based on a complete peripheral dropout with preproliferative signs in FA because of ischaemia. The criteria to perform peripheral panretinal scatter or PRP was thus below the criteria of the Central Vein Occlusion Study Group, which recommends PRP at the time an ischaemic patient develops 2 o'clock hours of iris neovascularization or any angle neovascularization.

Safety

An increase in IOP was noted in 12/73 DRP eyes (16.4%), in 2/15 (13%) of the patients with ischaemic CRVO, in 1/7 (14%) of the patients with nonischaemic CRVO and in 2/25 (8%) of the patients with BRVO at different follow-up examinations, defining IOP

rise over 20 mm Hg. The IOP rise was successfully controlled using topical antiglaucomatosa. Cataract extraction was required in 2/15 eyes (13%) of patients with ischaemic CRVO. In none of the RVO patient groups, a complete vitrectomy had to be performed because of vitreous bleeding, epiretinal gliosis or other reasons. Neither laser photocoagulation or cataract surgery or pars plana vitrectomy was performed in patients with nonischaemic CRVO (0%).

Adverse events like retinal detachment, sterile or nonsterile endophthalmitis, acute glaucoma, vitreous bleeding or haemorrhage did not occur in any of the patient groups.

Summary of the results

Single combined intravitreal triamcinolone and bevacizumab injection produced a gain in BCVA of 0.14 lines among 73 eyes studied for 24 weeks, when combined with the vitrectomy, as performed in this pilot case series. Overall, the effects of our pharmacological therapy presented here are difficult to compare with the three other (peer reviewed published) studies on combined intravitreal bevacizumab and triamcinolone injections as some report about treatment for refractory DME (Ahmadiéh et al. 2008), while others, like Soheilian et al., treated primary DME, like we did. Moreover, we

incorporated a higher dosage of triamcinolone (8 mg versus 2 mg) because of the presumed increase in drug clearance related to limited core vitrectomy. A statistically significant reduction in macular thickness was thus however rapidly achieved in all our patients and was sustained throughout the follow-up period reaching for all patients a plateau effect after 8 weeks, which could not be demonstrated by Soheilian et al. (2009) after 12 weeks with 2 mg triamcinolone without a vitrectomy. At the same time, a better BCVA improvement was observed in our patients that we grouped differently (macular ischaemia or no ischaemia) than the other three authors, which are briefly displayed in Table 3.

There was no need to retreat the macular ischaemic patients at T3 with the pharmacosurgery regimen more often than the group of NPDR without macular ischaemia (Fig. 2). This may relate to the fact that the NPDR without ischaemia respond better to the applied drugs, whereas lasercoagulation had to be carried out in only 56% at T3 of the proliferative patients, which would have experienced lasercoagulation in almost all cases even without the pharmacosurgery treatment.

In the eyes with ischaemic CRVO, intravitreal combined drug therapy led to a continuous increase in BCVA over 12 months (-0.53 versus baseline) and

Table 3. Comparable combination therapies in the treatment of diabetic retinopathy.

Study	BCVA of the combination treatment	Comment
Soheilian et al. (n = 150 eyes)	At 36 weeks, BCVA improved by -0.04 ± 0.33	At 12 weeks, no further beneficial effect of BV and TA than BV alone; no vitrectomy
Ahmadiéh et al. (n = 37 eyes)	At 24 weeks, BCVA improved by -0.21 ± 0.19	BV and TA had earlier visual improvement than BV alone at 24 weeks; no vitrectomy
Faghihi et al. (n = 41 eyes)	At 16 weeks, BCVA improved by -0.09 ± 0.2	BV and TA led exclusively to a significant BCVA increase; no vitrectomy
Koss et al. (n = 73)	At 24 weeks, BCVA improved by -0.14 ± 0.18	1.5 ml mid- to posterior vitrectomy

BV, Bevacizumab; TA, triamcinolone (*2 mg; **8 mg); MPC, macular photocoagulation; BCVA, best-corrected visual acuity. Important clinical differences are indicated in bold.

to a significant reduction in the macular oedema (−36% at 50 weeks, T3). To date, intravitreal triamcinolone and bevacizumab combination therapy for macular oedema secondary to CRVO has been described only in one case report (Ekdawi & Bakri 2007). In a patient with CRVO refractory to either triamcinolone (2 × 4 mg) or bevacizumab (6 × 1.25 mg) treatment alone, two combination approaches with triamcinolone and bevacizumab with a 4-month injection-free interval led to a sustained decrease in macular oedema from 800 to 200 μm and an increase in visual acuity from 20/400 to 20/40.

In our case series, the combined therapy had to be repeated in all patients with nonischaemic CRVO and in 75% of the ischaemic CRVO patients at the end of the follow-up period. Further treatment included PRP in 7 of 15 eyes because of preproliferative signs, which was performed 2 weeks after the first retreatment.

It should be noted in this context, however, that eyes with ischaemic CRVO, if left untreated, usually undergo PRP more often to increase retinal blood flow, which however does not seem to have an effect on the perfusion of the compromised macula (Arvas et al. 2002).

In the patients with nonischaemic CRVO, a large decrease in macular thickness (−59%) and a continuous and steep increase in BCVA (−0.37 LogMar units) was observed over 36 weeks. Nevertheless the combined therapy was repeated in all patients because of a relapse in macular oedema exceeding 150 μm.

It may be reasonable to apply even earlier retreatments according to the 'hit hard and early' strategy, similar to the therapy using repeated bevacizumab injections, the most common way that helps to achieve macula oedema stabilization (Ferrara et al. 2007). No other kind of further treatment became necessary in the patients with nonischaemic CRVO, unlike in the patients with ischaemic CRVO or BRVO.

In the patients with BRVO and CRVO who were treated with intravitreal triamcinolone as well as intravitreal anti-VEGF, early retreatment appeared to be more effective (Oh et al. 2007; Wang & Song 2009; Rensch et al. 2009). Of 25 eyes with BRVO, nine

eyes underwent a retreatment using the combined therapy regimen after 36 weeks, so basically the strategy to treat early and repetitive was not necessary in our patients. A statistically significant increase in BCVA was already seen from 13 weeks after initial treatment, i.e. earlier than in patients with CRVO, with a tendency of ongoing improvement.

Perspectives in ophthalmology

Holekamp et al. reported that the intraocular oxygen tension is lower in patients with diabetes than in patients without diabetes (Holekamp et al. 2006), and that vitrectomy leads to a sustained and significant increase in intraocular oxygen supply (Holekamp et al. 2005). A limited posterior pole vitrectomy may induce an intraocular oxygen redistribution in favour of the posterior pole with reoxygenating effects for the compromised macula in DR (Stefansson et al. 1981; Stefansson 2001), which has been demonstrated lately in an albino rabbit model, where choroidal neovascularization (CNV) was induced (Herbert et al.; Effects of Combined- versus Monotherapy in CNV-Induced Albino Rabbits; Poster 743 at the annual meeting of the Association for Research in Vision and Ophthalmology, 3–7 May 2009, Ft Lauderdale, FL, USA). Furthermore would an induction of a posterior vitreous detachment increase the diffusion rate of all substances, including oxygen, drugs and VEGF after additionally removing the mid- and posterior vitreous cortex. The limited 1.5 ml of the posterior and central vitreous core vitrectomy seems to have similar results as the concentration of VEGF and anti-inflammatory agents such as interleukin 6 and monocyte chemoattractant protein (MCP) have been observed after core vitrectomy to be decreased significantly over the retreatment of the pharmacological regimen (Pfister et al.; Intravitreal Growth Factors in Combined Therapy. Poster 1918 at the annual meeting of the Association for Research in Vision and Ophthalmology, 3–7 May 2009, Ft Lauderdale, FL, USA).

The relationship between the macular oedema in RVO and the condition

of the vitreous was investigated in several studies. Takahashi et al. noted that macular oedema was significantly more frequent in eyes with vitreomacular attachment (93%) than in eyes with posterior vitreous separation or detachment (41%; $p < 0.01$) (Takahashi et al. 1997). At the same time, vitreomacular attachment is significantly more frequent in eyes with shorter axial lengths in patients with CRVO and BRVO than in control eyes (Ariturk et al. 1996). Saika et al. (2001) demonstrated the effectiveness of a surgical posterior vitreous detachment together with gas/air tamponade in macular oedema secondary to BRVO. Similarly, for eyes with cystoid macular oedema because of nonischaemic CRVO, vitrectomy appears to be a possibly effective treatment if posterior vitreous detachment is performed or enzymatically induced by vitreolysis (Furukawa et al. 2006; Sebag et al. 2007). The steady increase in BCVA in the ischaemic CRVO group seen in our pilot study may thus be explained by the reoxygenation effects in the macula after the limited posterior pole vitrectomy. This might be associated with an induction of the PVD, which we observed in 4/15 patients (27%) by OCT. As the examination of a PVD was a not a primary outcome measure and thus not thoroughly investigated in this study, we thrive for a separate study of this important aspect with the correlation of a B-scan and the OCT in the future. We presume, however, that BCVA could continue to increase further, because all retreatments were performed at the end of the follow-up time as VEGF and anti-inflammatory agents like interleukin 6 and MCP decreased significantly over the retreatment follow-up in RVO after this pharmacological regimen (Pfister et al.; Intravitreal Growth Factors in Combined Therapy; Poster 1918 at the annual meeting of the Association for Research in Vision and Ophthalmology, 3–7 May 2009, Ft Lauderdale, FL, USA).

Medical monotherapy as presented earlier works effectively for several weeks and warrants high retreatment injections to counteract the macular oedema relapse. To reduce this burden, current combination therapy studies demonstrate a trend of therapeutically effective enhancement or

prolongation if the follow-up was reasonably long enough.

Our pilot study in particular shows an improving or maintaining visual acuity tendency in most cases with few retreatments and a true alteration in the vitreous physiology (PVD, liquefaction), which might lead to a sustainable physiological effect. These impressions have led to an investigator-initiated prospective, randomized and controlled trial for the treatment of DME, which is currently ongoing. Trials with adequate evidence level for the RVO management are on the way.

Acknowledgements

The Adolf Messer Foundation, Königstein, Germany, supports the research group.

The authors have the following conflicts of interest in the subject presented: F.H. Koch and M.J. Koss have a potential conflict of interest in the subject matter presented. He has received funding from Insight Instruments, Stuart, FL, USA, for travel expenses with regard to scientific meetings and conferences. All remaining authors have no conflict of interest in the subject matter presented.

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Received on April 18th, 2009.
Accepted on May 12th, 2010.

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