

Alternative ways to optimize treatment for retinal vein occlusion with peripheral capillary non-perfusion: a pilot study

Opções alternativas para otimizar o tratamento da oclusão da veia retiniana sem perfusão capilar periférica (um estudo piloto)

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ABSTRACT

Purpose: We compared the efficacy and safety of ranibizumab versus ranibizumab plus scatter laser photocoagulation (SLP) in patients with chronic post-central retinal vein occlusion (CRVO) macular edema (ME).

Methods: This prospective non-randomized pilot study included 250 patients with peripheral retinal ischemia and CRVO-related ME. The mean follow-up period was 24.5 ± 6.5 months. The clinical assessments conducted included best corrected visual acuity, optical coherence tomography, and multi-field fluorescein angiography with measurement of the ischemic area. The study population comprised two comparable patient groups with peripheral retinal ischemia that received different treatments for post-CRVO ME: ranibizumab with peripheral SLP of capillary non-perfusion areas (Group 1); and Lucentis® monotherapy (Group 2). Data analyses were performed using Statistica 7 software suite and included the estimation of $x \pm \delta$ values and their dispersion and covariation coefficients at different stages of the study.

Results: Clinically significant retinal ischemia was detected in 175 (70%) patients, occupying an average of 435.12 ± 225.13 mm², i.e., 167.15 ± 45.16 optic disc areas. Peripheral ischemia was found in 125 patients, representing 50% of all patients with CRVO and 71.4% of all patients with ischemic CRVO. The mean number of ranibizumab injections in patients who underwent SLP was 3.5 ± 1.6. Patients treated with ranibizumab monotherapy for 24 months received 10.6 ± 2.5 injections. Functional and anatomic results were comparable in the two groups.

Conclusions: The combination of ranibizumab injections and peripheral SLP in capillary non-perfusion areas can significantly decrease the number of injections and reduce neovascular complications.

Keywords: Retinal vein occlusion; Ranibizumab; Ischemia; Laser coagulation; Visual acuity

RESUMO

Objetivo: A investigação centra-se na terapia de edema macular pós-oclusão da veia retiniana central (OVCR) em casos com isquemia retiniana periférica. O objetivo foi comparar a eficácia e a segurança do tratamento com ranibizumab vs ranibizumab + fotocoagulação com laser de dispersão (SLP) em pacientes com edema macular crônico secundário a oclusão da veia retiniana central isquêmica.

Métodos: O estudo prospectivo não-randomizado incluiu 250 pacientes com isquemia retiniana periférica e edema macular relacionados a oclusão da veia retiniana central. O tempo médio de seguimento foi de 24,5 ± 6,5 meses. A avaliação clínica incluiu acuidade visual melhor corrigida, tomografia de coerência óptica (OCT) e angiografia por fluoresceína multi-campo com a medição da área de isquemia. A população estudada foi constituída por dois grupos de pacientes comparáveis com o oclusão da veia retiniana central isquêmica, que receberam tratamento diferente. Em nossa prática anterior, utilizamos ranibizumab (Lucentis®) em monoterapia (de acordo com a licença do medicamento) para edema macular pós-oclusão da veia retiniana central com isquemia retiniana periférica (Grupo 2). Mais recentemente, começamos a combinar ranibizumab com SLP periférica de áreas não perfusão capilar (Grupo 1). As análises de dados foram realizadas com o software Statistica 7 e incluíram a estimativa dos valores de $x \pm \delta$ e seus coeficientes de dispersão e covariância em diferentes estágios do estudo.

Resultados: Identificou-se isquemia retiniana clinicamente significativa em 175 (70%) pacientes, atingindo uma média de 435,12 ± 225,13 mm², ou seja, 167,15 ± 45,16 áreas de disco óptico. Isquemia periférica foi encontrada em 125 casos, representando 50% de todos os pacientes com oclusão da veia retiniana central e 71,4% de todos os pacientes com oclusão da veia retiniana central isquêmica. O número médio de injeções de ranibizumab em pacientes com SLP foi de 3,5 ± 1,6. Os pacientes tratados com ranibizumab em monoterapia durante 24 meses receberam 10,6 ± 2,5 injeções. Os resultados funcionais e anatômicos foram comparáveis nos dois grupos.

Conclusões: A combinação de injeções de ranibizumab com SLP periférica em áreas de não-perfusão capilar pode diminuir significativamente o número de injeções e reduzir as complicações neovasculares.

Descritores: Oclusão da veia retiniana; Ranibizumab; Isquemia; Fotocoagulação a laser; Acuidade visual

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common vascular condition capable of causing irreversible vision loss⁽¹⁾. Reduced visual acuity (VA) in patients with RVO is usually because of macular edema (ME) and/or locally impaired capillary perfusion⁽²⁻⁷⁾. Both the

location and total area of capillary non-perfusion greatly affect the duration of the disease and risk of proliferative complications⁽⁶⁻¹⁰⁾. Post-occlusion ME is typically caused by local inflammation and the effects of increased Vascular Endothelial Growth Factor (VEGF) levels^(2,6-10). VEGF expression is potentiated by tissue pH and the par-

Submitted for publication: November 16, 2016

Accepted for publication: February 5, 2017

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Funding: No specific financial support was available for this study.

Disclosure of potential conflicts of interest: None of the authors have any potential conflict of interest to disclose.

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Approved by the following research ethics committee: Pavlov First St. Petersburg State Medical University.

tial pressure and concentration of oxygen; hence, hypoxia induces VEGF synthesis in ischemic RVO⁽²⁾.

Previously, the relative incidences of ischemic versus non-ischemic RVO were reported to be 19% and 81%, respectively⁽¹¹⁾. Since the implementation of wide-field fluorescein angiography (FA) in clinical practice, it has been established that 60%-80% of patients with RVO have large areas of capillary non-perfusion in the mid- and far-peripheral retina, occupying 41-415 mm² (23-348 optic disc areas)^(12,13).

In most of these patients, foveal function is preserved, which explains the rapid improvement in their VA if treated with inhibitors of angiogenesis. However, when prescribing ranibizumab for RVO-related ME, certain limitations specified in its *Summary of Product Characteristics (SPC)* must be considered. The *SPC* for ranibizumab states that there are limited data on its use to treat patients with prior episodes of RVO or patients with ischemic branch RVO or central RVO (CRVO), and that its administration is not recommended in patients with RVO presenting clinical signs of irreversible ischemic loss of visual function⁽¹⁴⁾. In other words, RVO-associated ischemic maculopathy is a contraindication for the use of ranibizumab. However, whether this is true for peripheral ischemic retinopathy remains unknown. A recent study suggested that prolonged use of anti-VEGF agents decreases the rate of progression of retinal ischemia and reduces neovascularization (without reducing the risk of its occurrence) in patients with CRVO at high risk of iris neovascularization⁽¹⁵⁾. In our opinion, the optimal treatment for patients with peripheral ischemia and RVO is ranibizumab therapy combined with scatter laser photocoagulation (SLP) of non-perfused areas of the retina. We suggest that this combination shortens the treatment period and lowers the risk of neovascular complications, both of which reduce the cost of rehabilitation^(12,16).

Panretinal laser photocoagulation is the gold-standard therapy for ischemic CRVO complicated by iris and/or angle neovascularization⁽¹⁾. However, it does not improve vision or resolve ME. CRVO investigators propose the exclusive use of classical panretinal laser photocoagulation (including for early and preventive treatment), whereas we only use selective SLP of non-perfused areas⁽¹⁾.

Anti-VEGFs are also used to treat post-CRVO ME, although they have no beneficial effect on ischemia and fail to prevent neovascularization in some patients. In this study, we sought to identify a com-

bined therapy that caused as little laser injury as possible to improve VA without adverse effects.

METHODS

In this prospective study, we enrolled 250 patients with CRVO (135 women, 115 men; mean age, 62.4 ± 12.5 years) treated at the Ophthalmology Department of the First Pavlov State Medical University of St. Petersburg, St. Petersburg, Russia, between 2010 and 2014. The mean interval between disease onset and treatment initiation was 1.5 ± 1.2 months, and the average follow-up period was 24.5 ± 6.5 months. Patients were eligible for inclusion if they had: experienced an episode of CRVO in the preceding 6 months; a VA of ≥ 0.02 on the Snellen chart; and a central retinal thickness (CRT) of $\geq 450 \mu\text{m}$. Patients were excluded if they: were aged under 18 years; were pregnant; had suffered uncontrolled arterial hypertension, stroke, or myocardial infarction in the preceding 12 months; or had ocular inflammation, media opacity, or unstable primary glaucoma.

Retinal optical coherence tomography was performed at the first visit and repeated monthly during the follow-up period (SPECTRALIS® OCT; Heidelberg Engineering GmbH, Heidelberg, Germany). FA was performed at the first appointment in all patients and repeated at Months 3, 6, 12, and 24-26 in patients with retinal ischemia (Heidelberg Retina Angiograph 2; Heidelberg Engineering). We measured the non-perfused area in every angiographic image of the nine to 13 angiograms necessary to observe most of the retina with a 55° lens (therefore, the term multi-field FA is appropriate) and calculated the total non-perfused area (Figure 1). Two FA specialists separately outlined the non-perfused areas. Areas of non-perfusion were measured in mm² in unprocessed angiograms using pre-installed Heyex software v.1.7.0.0 (Heidelberg Engineering). We did not perform any manual adjustments to calculate ischemic indices in contrast to other researchers⁽¹⁷⁾.

Data analyses were performed using the Statistica 7 software suite (StatSoft, Tulsa, OK, USA) and included the estimation of $x \pm \delta$ values and their dispersion and covariation coefficients at different stages of the study. Differences were considered significant at $p < 0.05$.

After examination, patients were divided into three groups based on CRVO type: non-ischemic (those who received ranibizumab treatment and were not included in further comparisons and analyses);

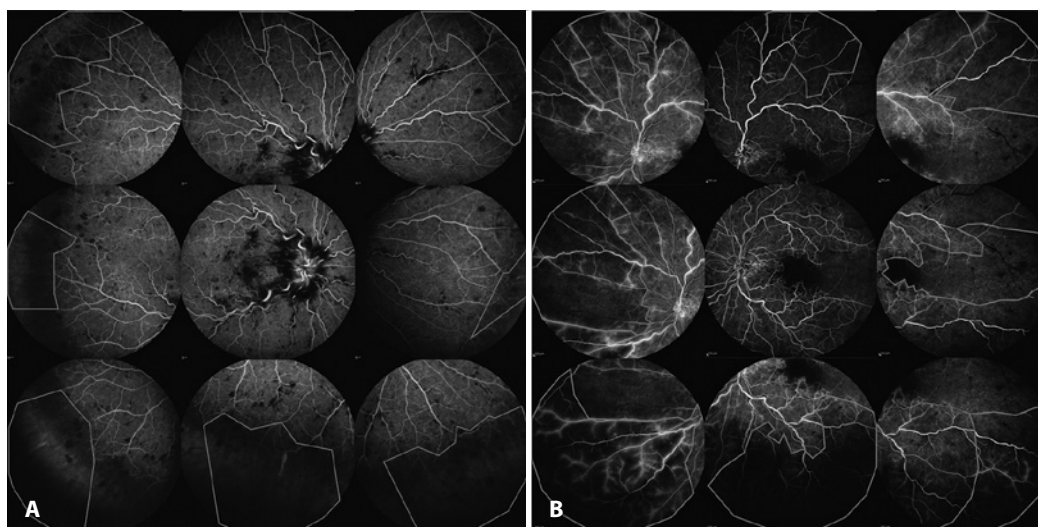


Figure 1. (A) and (B) Areas of capillary non-perfusion outlined in nine standard angiographic images from two different patients. To avoid overstating the total area involved because of the overlap of neighboring images, anatomic structures (such as blood vessels) were used as landmarks.

and two comparable (Table 1) ischemic groups that received different treatments. Patients with 10 disc areas or more of retinal capillary non-perfusion were considered to have ischemic CRVO.

Non-ischemic patients with CRVO received intravitreal injections of 0.5 mg ranibizumab scheduled as recommended by the manufacturer (Lucentis®; Novartis Pharma AG, Basel, Switzerland). This group was only examined to determine the prevalence of ischemia among patients with CRVO according to wide-field angiography results, and was not included in further analyses.

Group 1 received combined treatment: intravitreal injections of 0.5 mg ranibizumab every month for a 3-month period and selective peripheral SLP of non-perfused areas of the retina. SLP sessions were performed 30 min before the first intravitreal injection in all patients and repeated at months 1 and 2 as needed. The following settings were applied: laser wavelength, 514 nm; spot diameter, 400 µm; exposition, 0.15 s, and an energy level sufficient to produce a white coagulate. In some patients, we were unable to perform selective peripheral SLP of all the non-perfused areas in one session (for example, if the non-perfused area was too large and the patient experienced too much pain, or if we had to wait until hemorrhages had resolved in the retina). Laser treatment was then repeated at months 1 and 2, according to the opinion of the laser and FA specialists. It should be noted that this approach can leave a considerably large non-perfused area untreated for a relatively long time, which can interfere with VA and CRT. However, the main reason for "deferred" SLP was the presence of retinal hemorrhages, and it was impossible to apply complete SLP before they had resolved (a process that takes up to 3 months). If all non-perfused areas were coagulated in one SLP procedure, SLP was not repeated unless the non-perfused areas were found to have increased at follow-up FA.

Following the administration of the first three monthly intravitreal injections, which was after the patients had completed laser treatment, ranibizumab therapy was continued *pro re nata* (PRN) for another 24 months. An additional injection was considered necessary in patients who demonstrated retinal thickening of ≥ 150 µm and related significant vision loss. We defined a "significant" VA decrease as a loss of at least two lines on the Snellen chart in patients whose maximum achieved best corrected visual acuity (BCVA) was ≥ 0.4 , and a loss to 0.05 in those whose maximum BCVA was 0.1 on the Snellen chart. In patients with a VA > 0.1 and < 0.4 , reinjection was performed if there was a loss of one line on the Snellen chart.

Table 1. Baseline characteristics of the patients and data on the study outcome

Characteristic	Ranibizumab and SLP group (#1) n=88	Ranibizumab alone group (#2) n=87	p value
Baseline			
Mean age, years	62.50 ± 12.90	61.70 ± 11.40	0.38
Female sex, n (%)	52 (59.1)	53 (60.1)	0.41
Disease duration, months	1.40 ± 1.10	1.60 ± 1.30	0.34
Retinal ischemia area, mm ²	410.20 ± 157.25	425.50 ± 210.14	0.28
BCVA, Snellen chart	0.25 ± 0.15	0.27 ± 0.09	0.26
CRT, µm	524.02 ± 243.85	535.04 ± 210.12	0.32
Outcome			
BCVA by month 28, Snellen chart	0.41 ± 0.25	0.40 ± 0.15	0.29
CRT by Month 19*, µm	270.52 ± 123.81	287.04 ± 130.44	0.19
Mean number of ranibizumab injections	3.50 ± 1.60	10.60 ± 2.50	<0.01

Optical coherence tomography was performed in only a few patients between 19 and 28 months; therefore, we did not include these data in the analysis.

BCVA= best corrected visual acuity (assessed using a Snellen chart); CRT= central retinal thickness assessed by optical coherence tomography; SLP= scatter laser photocoagulation.

Patients in Group 2 received monthly ranibizumab monotherapy for the first 3 months and switched to a PRN regimen for the following 24 months.

These treatment regimens and reinjection criteria were selected for economic reasons. In Russia, patients with RVO receive no reimbursement for Lucentis® treatment (and use of intravitreal Avastin® [F. Hoffmann-La Roche Ltd, Basel, Switzerland] is prohibited). Therefore, many prefer to wait as long as possible for treatment based on their individual threshold. Thus, patients requested therapy when their vision was very poor. The rationale for the three monthly doses at the start of treatment was that we continued fixed monthly dosing until the improvement in VA was stable on two consecutive visits (in many patients, this occurred at months 2 and 3 or 3 and 4) and started PRN treatment after that. The mean number of injections administered with a fixed regimen was three.

The eye function and edema of patients in this study were worse than those of patients in the CRUISE study, in which no patients with ischemic RVO were included⁽¹⁸⁾. The conventional criteria of a VA < 0.5 and CRT ≥ 250 µm were therefore not applicable. According to these criteria, we should have used fixed dosing for a longer period, which our patients could not afford.

RESULTS

Multi-field angiography revealed capillary non-perfusion in 175/250 patients with CRVO (70%). Thus, Group 1 comprised 88 patients and Group 2 comprised 87 patients. The mean total area of retinal ischemia was 435.12 mm² (standard deviation [SD], ± 225.13 mm²), i.e., 167.15 optic disc areas (SD, ± 45.16). We diagnosed peripheral ischemia in 125 patients, corresponding to 50% of the total number of patients with CRVO and 71.4% of patients with any type of ischemia. The mean total area of peripheral retinal ischemia was 370 mm² (SD, ± 113.5 mm²), i.e., 142.21 (SD, ± 85.12) optic disc areas.

In Group 1, the mean VA at baseline was 0.25 ± 0.15 , and the mean central macular thickness was 524.02 ± 243.85 µm. In the PRN treatment period (24 months), patients in this Group received on average 3.5 ± 1.6 intravitreal ranibizumab injections. This means that a large proportion of patients in this Group received only the loading dose in the 2-year follow-up period. The average number of laser burns was 1320 ± 245 . After the third injection, VA usually reached its maximum (0.52 ± 0.15), and the central macular thickness decreased to 270.7 ± 151.34 µm. In a month, these parameters had decreased in all patients, reaching 0.41 ± 0.25 µm and 270.5 ± 123.8 µm, respectively, by the end of treatment. There were, however, 12 patients in whom the area of impaired capillary perfusion increased by 25–60 mm² over the total observation period, necessitating additional laser treatment. There was no correlation between the progression of ischemia and the number of injections.

The average number of injections administered after peripheral SLP sessions was 2.9 ± 1.4 . There was no correlation between final VA or final CRT and the total number of injections. As expected, a positive statistical relationship was found between the area of ischemia and the number of laser burns, as well as between the area of ischemia and CRT (both initial and final). Importantly, by the end of the study, this Group had reduced in number by three patients. One of them received an insufficient number of peripheral SLP sessions, and presented at Month 15 with neovascular glaucoma and eye pain, necessitating diode laser transscleral cyclophotocoagulation and panretinal photocoagulation (PRP); data from the other two patients were unavailable.

Patients in Group 2 received an average of 10.6 ± 2.5 intravitreal injections during the 24-month period. In this group, the mean VA at baseline was 0.22 ± 0.2 (Snellen chart), and the mean central macular thickness was 626.13 ± 298.06 µm. The highest VA and lowest retinal thickness, 0.45 ± 0.21 and 290.7 ± 214.5 µm, respectively, were registered after the third injection.

By the end of the study, 15 patients demonstrated a $45.5 \pm 15.6 \text{ mm}^2$ increase in the area of ischemia. Iris neovascularization occurred in five patients an average of 2.5 months after the completion of ranibizumab therapy, necessitating PRP (in two patients, diode laser transscleral cyclophotocoagulation was also performed). Two other patients developed posterior segment neovascularization and underwent additional treatment with PRP. Anterior segment neovascularization occurred in only one patient in Group 1. All other instances of neovascularization occurred in patients treated with ranibizumab alone (Group 2).

The dynamics of changes in VA differed between groups 1 and 2. In Group 1, VA was lowest at the 5-month follow-up and then remained generally stable, showing only minor fluctuations. In Group 2, VA showed no stabilization, and its fluctuations were large (Figure 2). CRT changes correlated well with VA changes (Figure 3). In both ischemic CRVO groups, the initial and final VA, initial and final CRT, and number of anti-VEGF injections were positively correlated with the area of capillary non-perfusion.

DISCUSSION

The use of multi-field angiography for the primary assessment of patients with CRVO enables the detection of retinal ischemia in almost 70% of patients. In most patients, ischemic changes are located at the periphery of the retina. Their total area is usually large, occupying on average 370 mm^2 (SD $\pm 113.5 \text{ mm}^2$), i.e., 142.21 (SD, ± 85.12) optic disc areas. Patients who fall into this category are at higher risk of proliferative complications; therefore, specific ischemic RVO management algorithms should be followed.

Notably, foveal function is usually preserved in these patients, ensuring a response to anti-VEGF agents. Ranibizumab monotherapy, however, provides only temporary effects. After injections stop, patients' vision deteriorates again, and ME recurs. For a more stable result, further injections are required. However, further injections confer a higher risk of complications and increased medical costs, making this treatment unfeasible for our patients. In our study, even prolonged (24-month) anti-VEGF therapy failed to reduce the risk of neovascularization. However, we found no correlation between the

number of ranibizumab injections and progression of ischemia in any of our patients. When combined with selective SLP of non-perfused areas of the retina, invasive intravitreal therapy can be minimized. The advantages of this approach include reduced medical costs, a shorter treatment period, and faster stabilization.

In a small randomized study, laser photocoagulation of peripheral areas of non-perfusion did not decrease injection frequency or improve VA in eyes with CRVO treated with ranibizumab⁽¹⁹⁾. The authors proposed that the complete loss of vascularity of the peripheral retina caused neuroretinal infarction and consequently no long-term VEGF production. Such patients may require less aggressive anti-VEGF treatment. However, there are many publications on the positive correlation between the area of non-perfusion and intraocular VEGF levels, and in our opinion it is essential to treat all patients with an ischemic retina.

Regarding patients in whom the non-perfused area showed progression over time, we consider the persistently reduced perfusion pressure between the arterial and venous vascular retinal network to be one of the main causative factors. Impaired Endothelin-1-induced autoregulation and neurovascular coupling may contribute to this process, with retinal venous pressure changes accompanying CRVO^(19,20). Further studies involving more patients and the measurement of perfusion pressure are needed to provide an answer to this question.

The main strengths of this pilot study are the number of patients observed and long follow-up period. The limitations of this study include the absence of randomization, probable ranibizumab undertreatment for local economic reasons, relative inaccuracy of BCVA measurements using the Snellen chart, and the possible "deferred laser" effect discussed in the Methods section. More experience in patients with peripheral ischemic CRVO over a longer follow-up period is needed.

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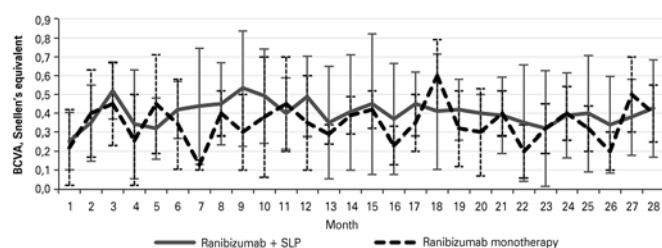


Figure 2. Mean visual acuity changes with 95% confidence intervals in groups receiving different therapies.

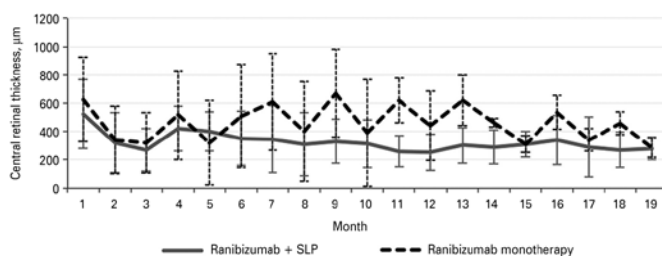


Figure 3. Mean central retinal thickness changes with 95% confidence intervals in groups receiving different therapies.

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Simpósio Internacional do Banco de Olhos de Sorocaba

26 a 28 de outubro de 2017

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