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Retinal oximetry during treatment of retinal vein occlusion by ranibizumab in patients with high blood pressure and dyslipidemia

Oxymétrie rétinienne au cours du traitement par ranibizumab de l'occlusion veineuse rétinienne chez les patients atteints d'hypertension artérielle et de dyslipidémie

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ABSTRACT

INTRODUCTION. In the present study, we examined retinal vascular oxygen saturation in patients with Retinal Vein Occlusion (RVO) presenting High Blood Pressure (HBP) and dyslipidemia before and during intravitreal anti Vascular Endothelial Growth Factor (anti-VEGF) inhibition (ranibizumab).

METHODS. We retrospectively reviewed the medical records of six patients with Visual Acuity (VA) reduced by Macular Edema (ME) secondary to RVO presenting HBP and dyslipidemia who underwent intravitreal injection of anti-VEGF between October 2014 and February 2015 in the department of ophthalmology of François Quesnay hospital at Mantes-la-Jolie (France). The main inclusion criterion was the presence of RVO with ME and declined VA . The primary endpoint was improvement of retinal venous oxygen saturation in patients with RVO before and 3 months after intravitreal ranibizumab injection. Secondary outcomes were improvement of retinal arterial oxygen saturation, improvement of Best Corrected Visual Acuity (BCVA) on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, regression of ME measured by the Central Macular Thickness (CMT) in nm and studying the correlation between blood pressure (BP) and retinal venous oxygen saturation before and after ranibizumab.

RESULTS. Six eyes of six patients were included. Before treatment, the mean (Standard Deviation, SD) of the retinal venous saturation (%) was $38,1 \pm 14,2$. Three months after injections, the mean (SD) of the retinal venous saturation (%) increased statistically significantly $49,2 \pm 11$ ($p = 0,03$).

CONCLUSION. In this study, retinal venous oxygen saturation in patient with RVO, HBP and dyslipidemia was partially normalized during intravitreal ranibizumab.

Key-words : Macular edema; retinal vein occlusion ; retinal venous oxygen saturation ; retinal oximetry ; optical coherence tomography; ranibizumab.

RESUME

INTRODUCTION. Nous avons évalué la saturation en oxygène de la vascularisation rétinienne chez les patients atteints d'Occlusion Veineuse Rétinienne (OVR) présentant de l'hypertension artérielle (HTA) et une dyslipidémie avant et pendant injection intravitréenne d'anti-Vascular Endothelial Growth Factor (anti-VEGF) (ranibizumab).

METHODES. Nous avons revu rétrospectivement les dossiers médicaux de six patients avec Acuité Visuelle (AV) diminuée en rapport avec un œdème Maculaire (OM) secondaire à une OVR et présentant de l'HTA et une dyslipidémie. Ces derniers ont reçu une injection intravitréenne d'anti-VEGF entre octobre 2014 et février 2015 dans le service d'ophtalmologie de l'hôpital François Quesnay à Mantes-la-Jolie (France). Le critère d'inclusion principal était la présence d'une OVR avec OM et diminution de l'AV. Le critère principal était l'amélioration de la saturation veineuse rétinienne en oxygène chez les patients atteints d'OVR avant et 3 mois après l'injection intravitréenne de Ranibizumab. Les critères secondaires étaient l'amélioration de la saturation artérielle rétinienne en oxygène, l'amélioration de la Meilleure Acuité Visuelle Corrigée (MAVC) sur l'échelle Early Treatment Diabetic Retinopathy Study (ETDRS), la régression de OM mesurée par l'épaisseur maculaire centrale (EMC)

en nm et d'étudier la corrélation entre la pression artérielle et la saturation veineuse rétinienne en oxygène avant et après ranibizumab.

RÉSULTATS. Six yeux de six patients ont été inclus. Avant le traitement, la moyenne (Écart-Type, ET) de la saturation veineuse rétinienne (%) était de $38,1 \pm 14,2$. Trois mois après les injections, la moyenne (ET) de la saturation veineuse rétinienne (%) a augmenté de manière statistiquement significative $49,2 \pm 11$ ($p = 0,03$).

CONCLUSION. Dans cette étude, la saturation veineuse rétinienne en oxygène chez les patients avec OVR présentant une HTA et une dyslipidémie était partiellement normalisée pendant le traitement par Ranibizumab intravitréen.

Mots-clés : œdème maculaire ; occlusion veineuse rétinienne ; la saturation veineuse rétinienne en oxygène ; oxymétrie de la rétine ; tomographie par cohérence optique; ranibizumab.

INTRODUCTION

Retinal Vein Occlusion (RVO) constitutes the second most common cause of retinal vascular disease after diabetic retinopathy. The prevalence of RVO is between 1% and 2% in patients older than 40 years [1]. The pathogenesis is multifactorial and still unclear. The prognosis of RVO is influenced by the location of the occlusion, by the extent of retinal non perfusion [2, 3, 4] and by the secondary Macular Edema (ME). The RVO can lead to irreversible visual loss.

When RVO occurs, retinal perfusion is impaired but does not stop, indicating that collateral outflow is considerably expanded. Collateral capacity in symptomatic cases is not enough to ward off an increase retinal venous pressure, venous dilation, retinal hemorrhage, retinal edema. Studies have shown a reduction in retinal venous blood flow after RVO. Reduction of blood flow leads to retinal hypoxia [5] and upregulation of Vascular Endothelial Growth Factor (VEGF), which would lead to vasodilatation and hyperperfusion. This response is inappropriate in RVO leading to ischemia and edema. Until intravitreal VEGF inhibitors became available it was unknown to which extent VEGF upregulation is responsible for the clinical manifestations of RVO. Hence, VEGF inhibition may improve retinal blood flow and oxygenation by promoting collateral formation or capillary perfusion. Intravitreal treatment with

ranibizumab reduces the progression of retinal capillary non-perfusion in RVO [6].

As a component of multimodal retinal imaging, studies show that oximetry may help produce an integrated overview of the pathophysiology of RVO and the effect of therapeutic VEGF inhibition [7, 8]. High Blood Pressure (HBP) is a universally agreed RVO risk factor. Other RVO risk factors, though not universally agreed upon, include advancing age, arteriolosclerosis, diabetes, dyslipidemia, blood hyperviscosity, thrombophilia, ocular hypertension and glaucoma.

However, no studies using oximetry has evaluated the effect of anti VEGF in patients with RVO and having two cardiovascular risk factors : HBP and dyslipidemia. Yet, it might help us to confirm the role of HBP and dyslipidemia in RVO. In the present study, we examined retinal vascular oxygen saturation in patients with RVO presenting HBP and dyslipidemia before and during intravitreal VEGF inhibition.

METHODS

We retrospectively reviewed the medical records of six patients with visual acuity (VA) reduced by ME secondary to RVO presenting HBP and dyslipidemia who underwent intravitreal injection of anti-VEGF between October 2014 and

February 2015 in the department of ophthalmology of François Quesnay hospital at Mantes-la-Jolie (France). Patients didn't have any treatment for HBP and dyslipidemia between October 2014 to February 2015. The main inclusion criterion was the presence of RVO with ME and declined VA . The diagnosis of RVO with ME was established on the retina funduscopy examination, on the Optical Coherence Tomography (OCT), the fluorescein angiography and the retinal oximetry. The decline in VA was assessed by the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. ME was defined in the spectral domain OCT. Exclusion criteria were chronic glaucoma untreated and uncontrolled, diabetes with retinopathy or diabetic maculopathy, periocular or ocular active infection, the diagnosis of uncontrolled systemic disease, epiretinal membrane, macular vitreoretinal traction syndrome that could prevent the improvement of VA, and laser therapy in the eye of study in the previous 3 months.

Before treatment, all patients underwent complete ophthalmologic evaluation including funduscopy examination, an assessment of Best Corrected Visual Acuity (BCVA) according to standardized ETDRS scale, tonometry, OCT (Heidelberg Engineering Spectralis[®], Spectral Domain OCT), fluorescein angiography and retinal oximetry. HBP was defined as blood pressure greater than 140/90 mmHg observed repeatedly during three successive consultations

over a period of 1 month. Dyslipidemia was defined on the basis of LDL cholesterol and High Health Authority (HAS) requirements. To find patient with RVO presenting dyslipidemia, we retrospectively reviewed their medical records. Patients had anti-VEGF injection in the eye of study after the initial visit. Patients with visual impairment due to macular edema secondary to Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) had injections of intravitreal ranibizumab. The recommended regimen consisted of three initial monthly injections of intravitreal ranibizumab 0.5 mg (Lucentis, Novartis AG, Basel, Switzerland), followed by retreatment as needed, guided by monthly clinical examinations including biomicroscopy, VA determination and OCT. Patients had retinal oximetry before and after treatment. All patients were examined monthly after the first injection for 3 months. A complete eye examination similar to that performed before treatment was done. Informed consent of all patients was obtained before treatment.

Retinal oximetry was performed with a prototype commercial instrument (Oxymap Retinal Oximeter P3, Oxymap ehf, Reykjavik, Iceland). Briefly, the device simultaneously acquires digital images at two wavelengths and automatically tracks retinal vessels on both images. Retinal vessel oxygen saturation is estimated by spectrophotometric analysis of light reflected from

retinal vessels and from the immediately surrounding retina. Oxygen saturation measurements were made on major temporal and nasal arteries and veins. A predetermined selection standardization protocol was used to minimize bias.

The primary endpoint was improvement of retinal venous oxygen saturation in patients with RVO before and 3 months after intravitreal ranibizumab injection.

The secondary outcomes was improvement of retinal arterial oxygen saturation, improvement of BCVA on the ETDRS scale, regression of ME measured by the Central Macular Thickness (CMT) in nm and studying the correlation between blood pressure (BP) and retinal venous oxygen saturation before and after ranibizumab.

P values for the analysis of the primary endpoint were obtained using the test of Wilcoxon signed rank, with $p < 0.05$ considered statistically significant.

RESULTS

Six eyes of six patients were included. Analysis of the patient's characteristics (Table 1) showed that the average age was 77.8 ± 4.4 years (mean $\pm$ standard deviation). The sex ratio was 1:1.

Before treatment, the mean (standard deviation, SD) of the retinal venous saturation (%) was $38,1 \pm 14,2$. Three months after injections, the mean (SD) of

the retinal venous saturation (%) increased statistically significantly $49,2 \pm 11$ ($p = 0,03$) (Table 2 and figure 1).

Regarding retinal arterial saturation (%), the mean (SD) was $94,1 \pm 6,2$ before treatment. The mean (SD) of the retinal arterial saturation did not change significantly during the treatment period $99,6 \pm 0,81$ ($p = 0,12$). Before treatment, the mean (standard deviation, SD) of BCVA was $59,8 \pm 11$. Three months after injections, the mean (SD) of the BCVA increased statistically significantly $72,2 \pm 8,6$ ($p = 0,03$). The mean of CMT (SD) was $495,6 \pm 135,2$ before treatment. Three months after injections, the mean (SD) of the CMT decreased statistically significantly to $268,6 \pm 57,8$ ($p = 0,03$) (table 3). Oximetry results on fellow eyes are not mentioned because they were normal and no RVO was found. Regarding tolerance, no cases of endophthalmitis or systemic side effects were highlighted. Blood pressure value at diagnosis for each patient is mentioned in table 4. Pearson correlation coefficient was calculated between blood pressure values and retinal venous saturation before and after intravitreal ranibizumab injection. There was a highly negative correlation between systolic blood pressure at diagnosis and retinal venous saturation at diagnosis $r = - 0,89$. There was a highly negative correlation between systolic blood pressure at diagnosis and retinal venous saturation after intravitreal ranibizumab injection $r = - 0,76$. There was a negative correlation between

diastolic blood pressure at diagnosis and retinal venous saturation at diagnosis $r = -0,58$. There was a negative correlation between diastolic blood pressure at diagnosis and retinal venous saturation after intravitreal ranibizumab injection $r = -0,60$ (figure 2, 3, 4, 5). LDL-cholesterol value for each patient is not mentioned because it was measured before the diagnosis of RVO by the general practitioner.

DISCUSSION

In this study, retinal venous oxygen saturation in patient with RVO was partially normalized during intravitreal ranibizumab treatment which is in agreement with previous studies [8, 9]. Retinal artery oxygen saturation was not reduced in eyes with RVO. Systolic and diastolic blood pressure at diagnosis was higher in patients with the lowest mean of retinal venous saturation before and after intravitreal ranibizumab injection. Systolic and diastolic blood pressure at diagnosis seems to be highly correlated to retinal venous saturation before and after intravitreal ranibizumab injection. No studies have, to our knowledge, evaluated the effect of ranibizumab on venous oxygen saturation in patients with RVO specifically associated with HBP and dyslipidemia. Our study shows that HBP and dyslipidemia did not modify the action of ranibizumab on retinal venous saturation improvement.

A limitation of this study is the lack of a control group and the small number of patients. Another limitation is the lack of comparison of retinal venous saturation with a group of patient presenting RVO without HBP and dyslipidemia. The duration of 3 months follow-up is less than some studies where it is around 6 months. Beyond this period, we found that monitoring was difficult because many patients were lost to follow-up. In addition, values of LDL-cholesterol are not mentioned.

It is unknown how retinal vessel oxygenation develops in the untreated eye with RVO and we therefore only have baseline values to compare with. VEGF inhibition has a dramatic effect on vascular leakage and retinal thickening in RVO. The physiopathology of the ME in RVO is different from the one that occurs after a cataract surgery [10]. There is reason to suspect that treatment may alter the normal course of vessel and perfusion vascular remodeling [11]. This includes reduction in arteriovenous passage time with increasing duration of RVO and capillary closure, with unchanged retinal blood flow but possibly a poorer oxygen extraction. Furthermore, evolution of venous saturation in BRVO is different than in CRVO. Studies have shown that in BRVO venous saturation is highly variable between patients: hypoxia is seen in some eyes but not in others [12]. This may reflect variable severity of disease, degree of occlusion, recanalization, collateral circulation, tissue atrophy, arteriovenous

diffusion or vitreal transport of oxygen. In our study, hypoxia was seen in all eyes with BRVO.

In conclusion, retinal venous saturation increase during treatment with intravitreal ranibizumab in patients with RVO associated with HBP and dyslipidemia.

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Declaration of interests

The present study received funding from Novartis, but the company had no role in the study design or study conduct.

Disclosure of interest

The authors declare that they have no competing interest.

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Tables and figures:

Table 1 : Characteristics of the study population

Table 2 : Primary outcome at 3 months

Table 3 : Secondary outcome at 3 months

Table 4 : Value of systolic and diastolic blood pressure and retinal venous oxygen saturation mean before/after intravitreal ranibizumab injection for each patient

Figure 1. Retinal venous oxygen saturation in central retinal vein occlusion (CRVO), at baseline and after 3 months ranibizumab treatment. The image shows the superior and inferior temporal vessel arcades in a CRVO affected eye at baseline (left) and the same eye after 3 months of treatment with intravitreal ranibizumab (right)

Figure 2. Correlation analysis between systolic blood pressure at diagnosis and retinal venous saturation at diagnosis

Figure 3. Correlation analysis between systolic blood pressure at diagnosis and retinal venous saturation after intravitreal ranibizumab injection

Figure 4. Correlation analysis between diastolic blood pressure at diagnosis and retinal venous saturation at diagnosis

Figure 5. Correlation analysis between diastolic blood pressure at diagnosis and retinal venous saturation after intravitreal ranibizumab injection

Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5

Tables :

Table 1.

Age (years)	77,8 $\pm$ 4,4 [°]
Female / male (%)	50/50*
Time between the injection and diagnosis (weeks)	2 $\pm$ 0,5 [°]
Right / left eye (%)	66,6/33,3*

[°] The more or less correspond to mean values +/- standard deviation

* Percentages are rounded, they do not always lead to a total of 100

Table 2.

	Pretreatment values	Values 3 months after the first injection	p values
Retinal venous saturation (%)	38,1 $\pm$ 14,2 [°]	49,2 $\pm$ 11 [°]	P = 0,03*

[°] The more or less correspond to mean values +/- standard deviation

* Statistically significant result p <0.05

Table 3.

	Pretreatment values	Values 3 months after the first injection	p values
BVAC (ETDRS score)	59,8 ± 11°	72,2 ± 8,6°	P = 0,03*
CMT	495,6 ± 135,2°	268,6 ± 57,8°	P = 0,03*
retinal arterial saturation (%)	94,1 ± 6,2	99,6 ± 0,81	P = 0,12

° The more or less correspond to mean values +/- standard deviation

* Statistically significant result p < 0.05

Table 4.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Retinal venous saturation mean (%) at diagnosis	12	34,4	38,7	45,7	45,9	52,2
Retinal venous saturation mean (%) after intravitreal ranibizumab injection	27,4	51,7	49,4	58,4	53,5	54,9
Systolic blood pressure (mmHg) at diagnosis	165	160	160	150	150	145
Diastolic blood pressure (mmHg) at diagnosis	95	90	95	85	80	90