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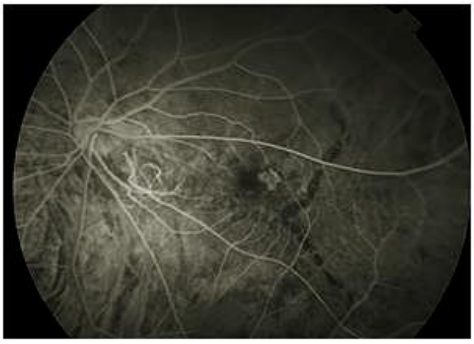
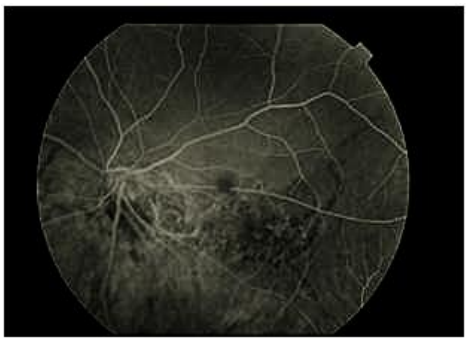
Traitement des membranes néovasculaires myopiques par ranibizumab : résultats à long terme.

Long-term follow-up of choroidal neovascularization in pathological myopia treated with intravitreal ranibizumab.





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RESUME

Introduction:

Etudier: 1) l'efficacité à long terme des injections intravitréennes (IVT) de ranibizumab dans le traitement de la membrane néovasculaire (MNV) du myope fort, 2) le rôle de l'imagerie multi-modale (tomographie en cohérence optique et angiographie fluorescéinique) et du changement d'acuité visuelle dans la décision de traitement avant chaque injection.

Matériel et méthodes:

Cette étude monocentrique, rétrospective, non-randomisée, a été réalisée à l'Hôpital Ophtalmique Jules Gonin de Lausanne. Elle a inclu les patients traités par IVT de ranibizumab pour MNV myopique suivis ≥24 mois. Après une dose de charge de 1 à 3 injections, le suivi se basait sur un traitement à la demande (pro re nata). L'examen ophtalmologique, la mesure de la meilleure acuité visuelle corrigée (MAVC), et la tomographie en cohérence optique (OCT) ont été réalisés à chaque visite, et l'angiographie fluorescéinique (AF) a été faite initialement et en cas de suspicion d'activité néovasculaire. Les critères de retraitement incluaient les métamorphopsies, la perte d'acuité visuelle de ≥5 lettres ETDRS, les signes d'exsudation à l'OCT et/ou à l'AF.

Résultats:

24 yeux de 24 patients ont été inclus avec un suivi moyen de 49 mois (25-84 mois). La MAVC moyenne a augmenté de initialement 62.8 ±13.8 lettres à 72.8 ±12.9 lettres à la dernière visite (p=0.001). Le nombre moyen d'injections était 2.2 la première année, et inférieur à 1 les années suivantes. Les sensibilités de l'AF, de l'OCT *spectral domain,* et de la perte de MAVC ≥5 lettres étaient respectivement 62.6%, 51.4%, and 40%. L'angiographie fluorescéinique montrait une sensibilité supérieure à l'OCT dans la décision de traitement (p=0.007).

Conclusions:

Les IVT de ranibizumab ont démontré une efficacité fonctionnelle à long terme avec un nombre réduit d'injections pour la MNV myopique. L'angiographie fluorescéinique a un rôle prépondérant dans la décision de traitement des MNV actives.

MOTS CLES

Ranibizumab, néovascularisation choroïdienne, myopie forte

TITLE

Long-term follow-up of choroidal neovascularization in pathological myopia treated with intravitreal ranibizumab.

Langfristige follow-up Daten intravitrealer Ranibizumab Therapie von choroidalen Neovaskularisationen bei hoher Myopie.

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ABSTRACT

Background:

To report our functional results of efficacy of intravitreal ranibizumab (IVR) for submacular choroidal neovessels (CNV) in high myopia, and to compare the role of optical coherence tomography (OCT), fluorescein angiography (FA) and visual acuity changes in the treatment decision prior to each injection.

Patients and methods:

This is a retrospective study performed in Jules Gonin Eye Hospital. It included all patients with myopic CNV treated with IVR injections with a minimal follow-up of 24 months. After an induction dosing from 1 to 3 injections, the follow-up was based on a PRN regimen. Ophthalmic evaluation, best corrected visual acuity (BCVA), and OCT were done at each visit, and FA at baseline and if neovascular activity was suspected. Retreatment criteria included metamorphopsia, visual loss of ≥5 ETDRS letters, any fluid on OCT and/or leakage on FA.

Results:

24 eyes were included in the study. Mean follow-up was 49 months. Mean BCVA improved significantly from 62.8 ±13.8 letters at baseline to 72.8 ±12.9 letters at last follow-up visit (p=0.001). The mean number of injections was 2.2 in the first year and below 1 for the following years. The sensitivity of FA, SD OCT, and BCVA loss ≥ 5 letters were 62.6%, 51.4%, and 40% respectively. The FA showed significant higher sensitivity in treatment decision than OCT (p=0.007).

Conclusion:

Our study showed that IVR provides a significant long term visual benefit in myopic CNV with a small number of injections. FA has a preponderant role in the treatment decision of active myopic CNV.

PRECIS

Our study showed long term efficacy of ranibizumab in the treatment of myopic CNV. We studied also the contribution of different modalities (OCT, FA and BCVA loss) in the retreatment decision.

ABSTRAKT

Hintergrund:

Ziel der Studie war es, die funktionellen Resultate von intravitrealem Ranibizumab (IVR) für submakuläre choroidale Neovaskularisationen (CNV) bei hoher Myopie zu beschreiben, und dabei die Rolle der optischen Kohärenztomographie (OCT), der Fluoreszein Angiographie (FA) und von Visus Veränderungen in Bezug auf die Behandlungsentscheidung zu untersuchen.

Patienten und Methoden:

Diese retrospektive Studie schloss Patienten ein, die im Universitätsspital Jules Gonin wegen myoper CNV mit IVR behandelt wurden und mindestens 24 Monate kontrolliert respektive behandelt wurden. Nach initialen 1-3 monatlichen IVR Dosen, wurden die Patienten gemäss einem pro re nata (PRN) Schema weiterbehandelt. Bei jeder Untersuchung wurde ein kompletter ophthalmologischer Status erhoben, die best korrigierte Sehschärfe (BCVA) gemessen, und ein OCT gemacht. Eine FA wurde zu Beginn

durchgeführt und bei Verdacht auf neovaskuläre Aktivität. Wiederbehandlungskriterien beinhalteten Metamorphopsien, einen Visusverlust von 5 oder mehr ETDRS Buchstaben, und/oder im OCT nachgewiesene Flüssigkeit, respektive exudative Aktivität in der FA.

Resultate:

Vierundzwanzig Augen mit mittlerer Nachbeobachtungszeit von 49 Monaten wurden in die Studie eingeschlossen. Die Sehschärfe verbesserte sich im Mittel signifikant von initial 62.8 ±13.8 Buchstaben auf 72.8 ±12.9 Buchstaben bei der letzten Untersuchung (p=0.001). Die mittlere Anzahl IVR lag bei 2.2 im ersten Jahr und unter 1 in den Folgejahren. Die Sensitivität der FA, des OCT, und des BCVA Verlustes von 5 oder mehr Buchstaben lag bei 62.6%, 51.4%, respektive 40%. Die FA zeigte signifikant höhere Sensitivität bei der Wiederbehandlungsentscheidung als das OCT (p=0.007).

Schlussfolgerung:

Diese Studie zeigte langfristige und signifikante Visuserfolge der IVR Behandlung für myope CNV mit sehr geringer Anzahl von Injektionen. Die FA hat eine zentrale Rolle in der Wiederbehandlungsentscheidung bei aktiven myopen Membranen.

PRECIS

Diese Studie evaluiert die Langzeitresultate der Ranibizumab Behandlung für myope subretinal Membranen. Zudem wurde die Sensitivität von diversen Untersuchungsmodalitätet hinsichtlich der Wiederbehandlungsentscheidung evaluiert.

KEY WORDS

Ranibizumab, myopic neovascularization, anti-VEGF

INTRODUCTION

High or pathologic myopia (≥-6 diopters) is a major cause of visual impairment worldwide [1].

Choroidal neovascularization (CNV) occurs in 5 to 10% of the cases [2, 3]. In young patients, high myopia is the first cause of CNV[4]. Various studies showed that the natural history of this complication is unfortunately often poor [5, 6].

Since the 2000's, photodynamic therapy (PDT) was used to treat neovascularization with moderate benefits. The results at one year were very promising, but the results at 2 years [7] and more [1, 8] didn't report superiority compared to placebo.

Since 2006, intravitreal anti-vascular endothelial growth factor (anti-VEGF) drug gradually replaced PDT, and became since 2009 the first treatment in clinical practice [9, 10].

Many studies demonstrated a significant short term efficacy of anti-VEGF, with a mean visual acuity improving at 6 [11] and 12 months [12, 13].

Recently, two high-evidence phase II and III studies (respectively REPAIR [14] and RADIANCE [15] studies) have confirmed the very good prognosis at 12 months of patients treated by intravitreal ranibizumab (Novartis Pharma AG, Basel, Switzerland Lucentis®).

Fewer studies with a longer follow-up from 24 to 48 months also showed a functional benefit over time [16–20].

The purposes of this study were: 1/ to report our long term functional results of efficacy of intravitreal ranibizumab for submacular neovessels in high myopia and 2/ to compare the role

of spectral domain optical coherence tomography (OCT), fluorescein angiography (FA) and visual acuity changes in the treatment decision prior to each injection.

METHODS

This is a monocentric retrospective nonrandomized study performed in the Jules Gonin University Eye Hospital of Lausanne including high myopic patients treated with intravitreal ranibizumab injections for submacular CNV with a minimal follow-up of 24 months after the first injection, from 2006 to 2013. Our study respects the tenets of Declaration of Helsinki and at the time of the first injection all patients gave an informed written consent regarding the off-label use of ranibizumab.

The database of the Medical Retina unit, the off-label ranibizumab invoicing and the operating room register were used for patient's identification. All folders were then reviewed by a retina specialist (AA) to confirm that the inclusion criteria were met.

Inclusion criteria were: 1/ presence of active sub- or juxta-foveolar subretinal neovessels secondary to high myopia defined as a minimal refractive error of 6 diopters (D), 2/ baseline BCVA ranging from 5 to 80 ETDRS letters, 3/ treatment with ranibizumab intravitreal injection, 4/ minimal follow-up of 24 months after the first injection defined as baseline.

Exclusion criteria were: 1/ PDT or laser treatment during the last 6 months before the first injection, 2/ prior intravitreal bevacizumab (Avastin®) injection, 3/ presence of foveolar atrophy on autofluorescence, 4/ presence of other ocular pathology that could interfere with the visual outcome during the study (epiretinal membrane, myopic foveoschisis, age related macular degeneration, and other diseases).

The initial examination included : BCVA measurement with Early Treatment Diabetic Retinopathy Study (ETDRS) charts, dilated fundus examination, autofluorescence, colour fundus photography, quantitative and qualitative macular measurement by time domain- or spectral domain-optical coherence tomography (TD-OCT Stratus OCT, Zeiss Inc; SD-OCT, Cirrus, Carl Zeiss Meditec, Inc., Oberkochen, Germany and Spectralis Heidelberg®, Heidelberg, Germany), and fluorescein angiography (FA) (TopCon TRC-50IX (Tokyo, Japan), Heidelberg HRA®, Heidelberg, Germany). Because OCT machines changed from time domain (TD) to spectral domain (SD) OCT, quantitative anatomical outcome could not be reported in our study.

BCVA measurement, fundus examination and OCT were performed at each visit and FA was performed only if needed.

Criteria to define an active neovascularisation were: 1/ recent vision loss of ≥ 5 letters and/ or recent metamorphopsia, 2/ new subretinal haemorrhage at funduscopy examination (in presence of a confirmed neovascular subretinal network on OCT and/or FA), 3/ intra- or subretinal fluid on OCT, and 4/ leaking neovascular network on FA.

The treatment regimen was dependent on the ophthalmologist in charge of the patient. After an induction dose of 1 to 3 injections, the follow-up regimen was based on a pro re nata (PRN) regimen: in case of recurrence (presence of one criteria of active neovascularisation at least) a single injection was performed with an examination one month later.

Injections were stopped when BCVA was stable over two consecutive follow-up examinations in absence of any exudative sign on fundus, OCT and FA (if performed).

To define the comparative contribution of any fluid on OCT, presence of CNV on FA, and BCVA change compared to the last visit in the treatment decision, we considered the set of

these 3 arguments along with the presence of subjective symptoms (metamorphopsia) as reference for all treatment decisions in real life setting. Thirty seven treatment decisions were analysed over the time of our study.

For this analysis, we included only the patients examined with SD-OCT from baseline (SD-OCT Cirrus or Spectralis Heidelberg). FA on Topcon Corp and Heidelberg HRA were pooled and analysed together whereas SD-OCT Cirrus and Spectralis were processed separately. FA and OCT were analysed separately by two different retina specialists (AA, AD) and another investigator (ML) reviewed BCVA change before each treatment decision.

The maximal duration between OCT and FA exams and treatment decision was 2 weeks.

Statistical analysis was performed using SPSS for Windows software (version 19.0, SPSS, Inc.). Descriptive analyses are reported as means standard deviation for continuous variable and as percentage for qualitative variables. BCVA at baseline, and different follow-up evaluations were compared using Wilcoxon test. The sensitivities of different modalities were reported as percentage, and compared using Fisher exact test. A 2-tailed probability of 0.05 or less was considered statistically significant.

RESULTS

Baseline characteristics

Twenty four eyes (24 patients) were included in this study. The mean patients' age was 57 years (range: 40-82). Male to female ratio was 0.55. The mean follow-up was 49 months (range: 25-84 months). Forty six percent of eyes were pseudophakic. The mean spherical equivalent at diagnosis was -16 diopters (range: -27 to -6 D). Three out of 24 included eyes (13%) were previously treated with PDT at least 6 months prior to baseline. All patients

showed an underlying lacquer cracks on FA at the time of diagnosis of active myopic CNV. The CNV was classic in 100% of cases, retrofoveal in 22 (92%) eyes and juxtafoveal in 2 eyes.

Visual outcomes

At baseline, the mean BCVA was 62.8 ±13.8 ETDRS letters. BCVA improved significantly to 71.7 ±14.7 ETDRS letters at 1 year (p= 0.001; n=24), 73.2 ± 10.7 ETDRS letters at 2 years (p= 0.001; n=24), 69.1± 11.7 ETDRS letters at 3 years (p= 0.005; n=15), and 68.7±12.3 ETDRS letters at 4 years (p= 0.012; n= 14). The mean BCVA at last follow up visit was 72.8 ±12.9 ETDRS letters (p=0.001). The BCVA changes over time are illustrated in Figure 1. Figure 2 illustrates the proportion of eyes who gained >5, >10, and >15 ETDRS letters at month 12, 24, 36, and 48 months. 20.8% and 41.7% of patients gained respectively ≥15 letters or ≥10 letters at 12 months (N=24). These results was maintained at 48 months follow up (n=14).

Number of injections

The mean number of injections during the first, second, third, and fourth year were respectively: 2.2, 0.4, 0.1 and 0.4 injections. Figure 3 shows the number of injections at month 24.

Anatomical outcome

At the last visit, 100% of the eyes showed absence of leakage and fluid on FA and OCT. 21% of eyes developed macular atrophy on autofluorescence when comparing baseline and last exams, 47% of eyes developed fibrosis on SD OCT.

Eyes with atrophy had longer follow-up (FU) period (mean 64.4 months) compared to eyes without atrophy (mean FU period 45 months; p=0.04). The mean number of injections was respectively 6.6 injections in eyes with atrophy and 2.8 in eyes without atrophy (p=0.13) There was no difference in the follow up period (mean FU= 51.9 months in eyes with fibrosis and mean FU= 47 in eyes without fibrosis; p=0.66) and in the number of injections (mean number of injections was 4.3 in eyes with fibrosis and 2.5 in eyes without fibrosis; p=0.97) between eyes which developed fibrosis or not.

Treatment decision

When compared to the gold standard for treatment decision which consisted of the combination of: presence of BCVA loss of ≥5 ETDRS letters, presence of any fluid on OCT and/or evidence of leakage on FA, the sensitivity of the different modalities was: 62.6% for FA, 53.8% for OCT performed with Cirrus, 45.5% for OCT performed with Heidelberg (the difference was not significant between the two OCT types; p=0.728), and 40% for objective vision loss of ≥5 ETDRS letters. This is illustrated in the figure 4. There was a significant difference in sensitivity between OCT and FA (p=0.007) (Figure 5).

Sensitivity of combined methods was 70.2% for OCT and/or FA, 73% for FA and/or vision loss of ≥5 ETDRS letters, and 60% for OCT and/or vision loss. There was concomitant positive findings on OCT and FA only in 43.3% of treatment decisions.

DISCUSSION

Various studies showed the efficacy of intravitreal anti-VEGF agent for treatment of myopic CNV in both short and long term follow up [11–21].

Our results correlate well with previously published long term studies. Indeed, we found that intravitreal ranibizumab injection provides a significant visual improvement sustained up to 4 years. The mean BCVA changes from 63 ETDRS letters at baseline, to 72 ETDRS letters at month 12, 73 ETDRS letters at month 24, and 69 ETDRS letters at months 36 and 48. In comparison, Franqueira et al.[16], in a retrospective study of 40 eyes using ranibizumab only, reported a mean visual improvement from 55.4 letters at baseline to 59.7 letters at month 12, 61.8 letters at month 24, and 63.4 letters at month 36. Hefner et al. [22] retrospectively studied 15 eyes treated with ranibizumab , and reported an improvement of mean BCVA from 50 letters at baseline to 70 letters at months 12, 24 and 36. A retrospective analysis of Ruiz Moreno et al. [23] studied 92 eyes treated by either bevacizumab or ranibizumab, and reported a mean BCVA change from 46.1 letters at baseline to 53.1 at month 48. They did not find a significant difference in efficacy between these two anti-VEGFs agents. Several other studies already showed no significant difference in term of vision improvement between bevacizumab and ranibizumab [11,17, 23]. In our study, the mean baseline BVCA was higher than in all previously mentioned studies. This could explain our relative small percentage of patient gaining ≥15 letters or more as compared with RADIANCE study [15]. Over time, a gradual loss in BCVA is observed in our cohort, and that could be related to degenerative retinal changes over time and/or to loss of follow-up of patients with good functional outcome.

The number of injections given during the follow-up of our patients was low with a mean of 2.2 injections in the first year and less than one injection thereafter. These results are consistent with other studies (such as REPAIR and RADIANCE studies) where the mean number of injections during the first year was respectively 1.9 injections (REPAIR), 4 injections (RADIANCE subgroup that received 2 IVR as loading dose) and 2 injections (RADIANCE subgroup that received one IVR as loading dose) [14, 15]. In addition, 83% of patients received a maximum of 3 injections at 24 months compatible with a significant

functional benefit. These findings obviously contrast with results reported in exudative macular degeneration treated with repeated anti-VEGF injection. Indeed, the chronic degenerative changes underlying wet age-related macular degeneration are not present as such in myopic neovascularisation. This rapid initial benefit was also found in REPAIR and RADIANCE studies [14, 15]. These results are encouraging for patient counselling when started on anti-VEGF therapy. The small number of injections per year seems to valuate a PRN treatment regimen starting from baseline in clinical practice.

Twenty one percent of our patients developed macular atrophy on autofluorescence during the follow-up. Patients with atrophy had an overall longer follow-up and higher number of injections when compared to the whole cohort. Peiretti et al [20] reported 33% of atrophy after 4 years. Yoshida et al. [24] reported that in the natural course of high myopic patients 96.3% developed atrophy on colour fundus photographs or FA after 10 years. Besides the natural evolution, the higher number of injections may contribute to atrophy progression. In the CATT study [25], patients on monthly treatment showed higher progression of geographic atrophy over time. Even if the physiopathology of exudative age-related macular degeneration and myopic neovascularisation is different, accumulation of anti-VEGF drug in the retinal pigmentar epithelium [26] can have toxic effect in both conditions.

Peiretti et al. reported fibrosis in 71% of treated eyes at 4 year. 47% of our patients developed fibrosis at the last visit. In both series, fibrosis overcomes the development of geographic atrophy. This finding is in accordance to the type 2 CNV mostly found in CNV patients [27]. In our cohort, all patients had a classic CNV. Our results showed that fibrosis was not related to time of follow-up, what is confirmed in the retrospective study of Lai et al. [17] who analysed visual outcome of 37 treatment-naïve eyes treated by ranibizumab or bevacizumab and reported 56.8% of fibrosis at 3 months. This suggests a potential role for combined anti-PDGF [28, 29] and anti-VEGF as baseline treatment of myopic CNV.

Multimodal imaging is today the gold standard to confirm the diagnosis of active CNV in pathological myopia. Our analysis showed the higher sensitivity of FA for treatment decision (62%). Leveziel et al [30] also reported a high sensitivity of FA (82%). His study investigated the role of imaging only at baseline visit for active CNV which may explain the difference between these two results. SD-OCT and FA signs of activity might be more obvious at baseline than during the follow-up.

OCT analysis found no significant difference between Cirrus and Heidelberg SD-OCT sensitivities. Sensitivity was 53.8% for Cirrus OCT and 45.5% for Heidelberg OCT. Cirrus OCT was mostly performed at the beginning of the study, then Spectralis SD-OCT progressively replaced in our clinical practice by. Leveziel et al. [30] reported a sensitivity of 48.6% for Heidelberg SD-OCT in the diagnosis of new myopic CNV on OCT. Both studies showed a superiority of fluorescein angiography over OCT in the treatment decision of myopic CNV. Sensitivity of combined methods was the highest (73%) for FA and/or vision loss and was only of 60% for OCT and/or vision loss. This last combination may reflect the overall routine clinical practice in most places. Concomitant positive findings on OCT and FA were met in only 43.3% of treatment decisions. Leveziel et al. mentioned an even lower agreement between FA and OCT of 16.1%. This illustrates well that FA cannot simply be replaced by SD-OCT in clinical practice and that FA still play a major role in the management of myopic CNV.

Our study has limitations including a relatively small number of eyes and the monocentric retrospective design. The absence of control group for analysis of treatment decision specificity was also a limitation.

In conclusion, our 4-year results analysis of patients with high myopic CNV treated by intravitreal ranibizumab injection on a PRN regimen confirmed an excellent long term visual prognosis with a low number of injections. Long term anatomical evolution showed subfoveal

fibrosis in half of our patients suggesting a role for combined anti VEGF-anti fibrotic drug.

The role of fluorescein angiography remains preponderant in the treatment decision of CNV due to high myopia.

FIGURES

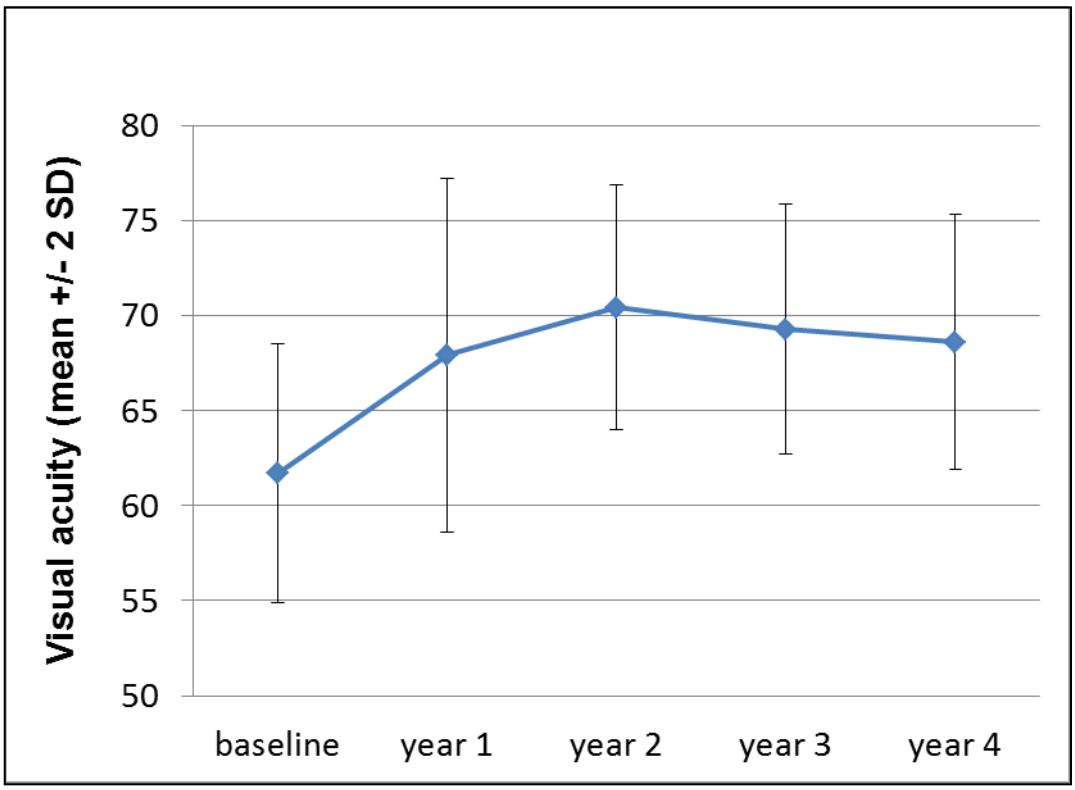

Figure 1. Mean visual acuity change over time

This graph shows the mean visual acuity change over time. Mean VA gain was 9±15, 10±9, 6±9, 6±9 letters at 1, 2, 3, 4 years respectively. The mean visual improvement at last visit was significant (p=0.001).

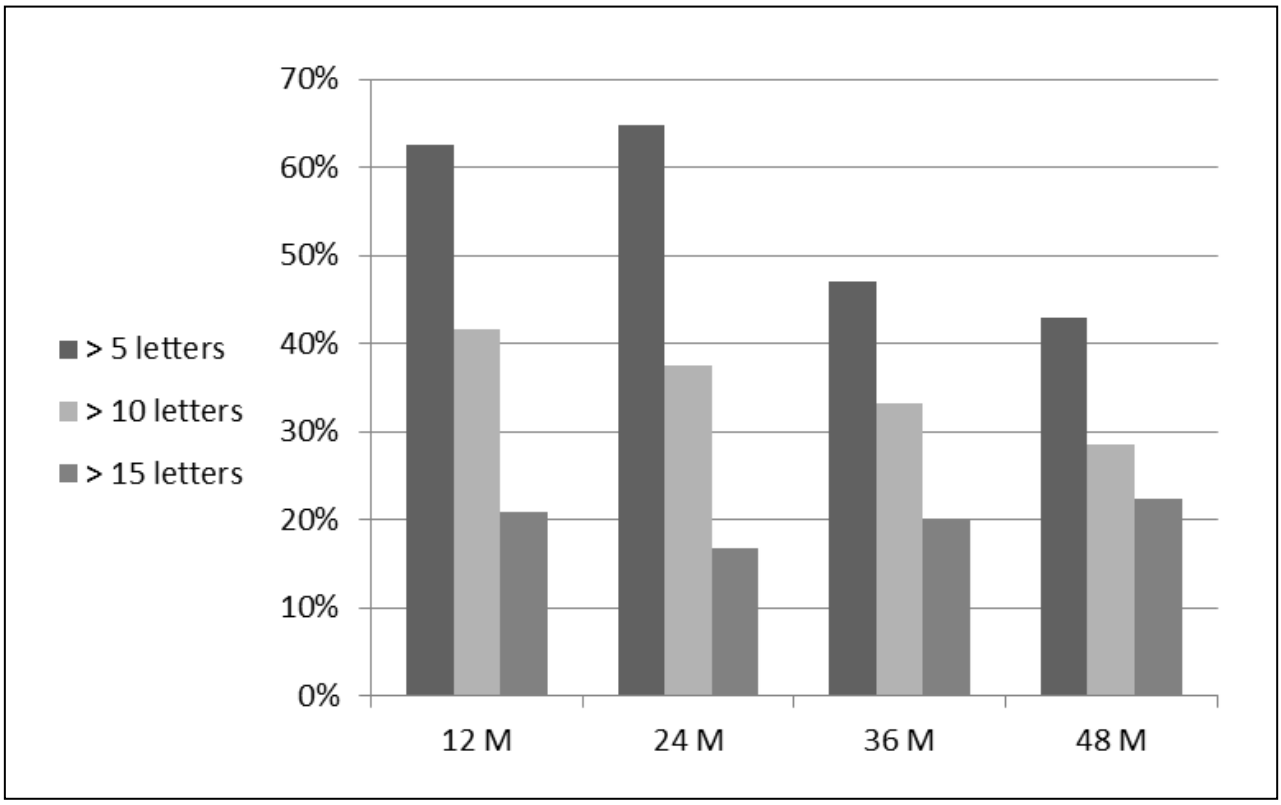

Figure 2. Vision gain at 12, 24, 36 and 48 months

This figure represents the percentage of eyes gaining >5, >10, and > 15 ETDRS letters at 12, 24, 36, and 48 months.

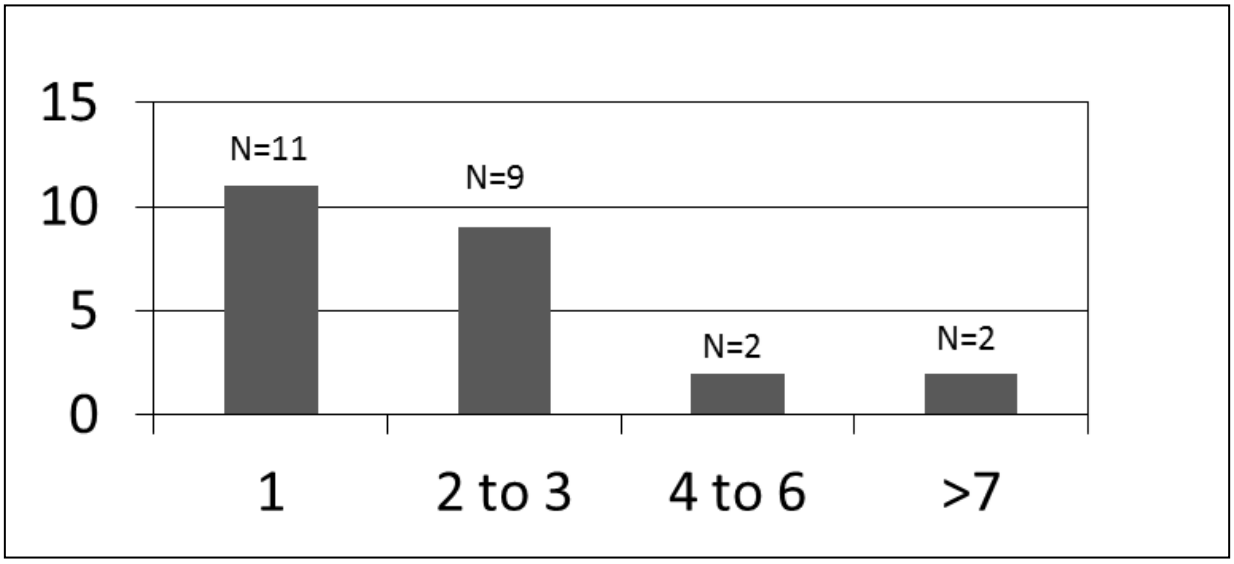

Figure 3. Number of injections at month 24

This figure shows the number of patients (N) who necessitated 1, 2-3, 4-6, and more than 7 injections at month 24. 83% of patients received a maximum of 3 injections at month 24.

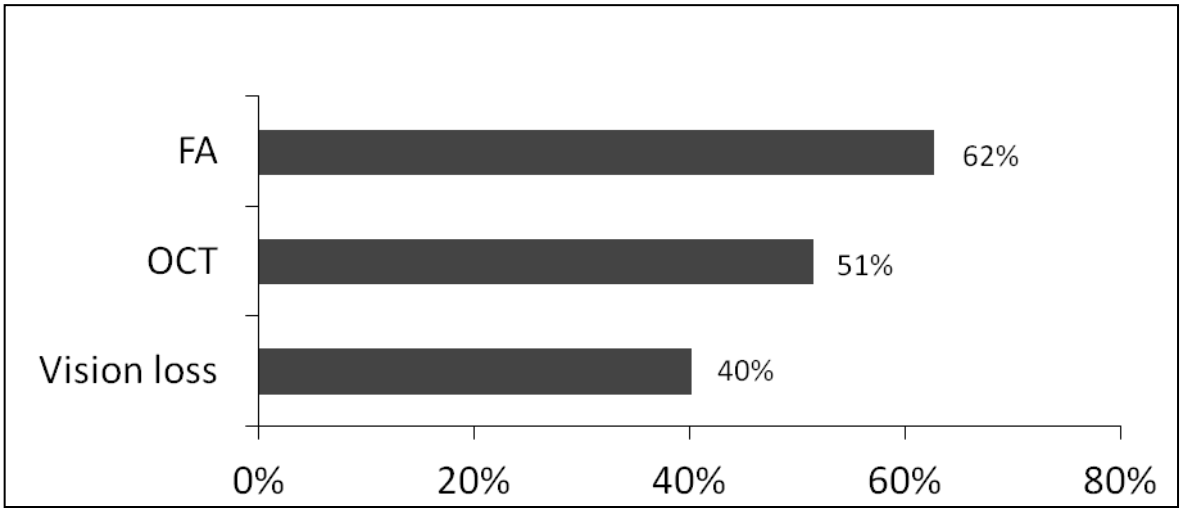

Figure 4. Sensitivity of FA, OCT and vision loss of ≥5 ETDRS letters for decision of treatment.

Fluorescein angiography was the most sensitive modality in the treatment decision. The difference in sensitivity between OCT and FA was significant (p=0.007).

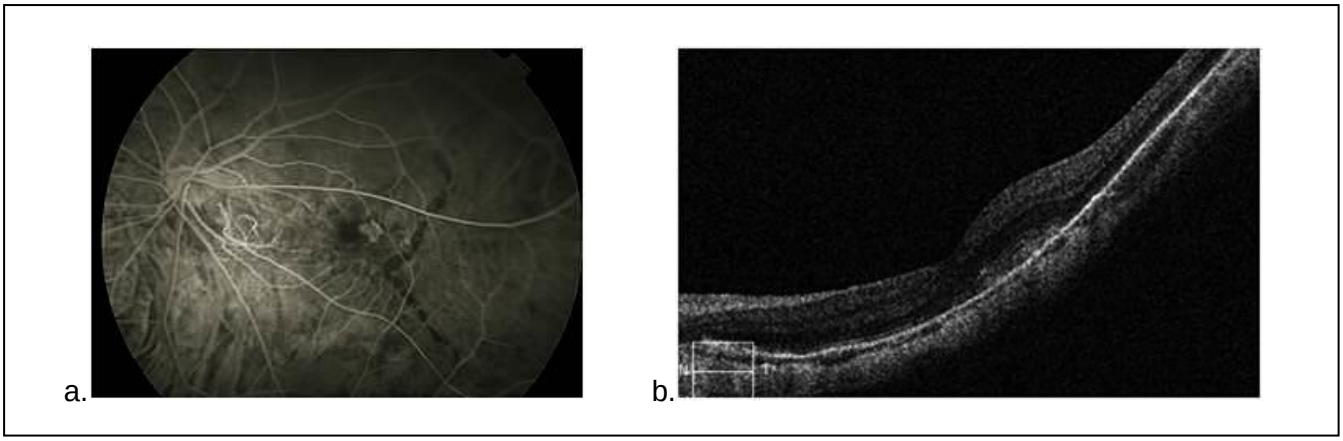

Figure 5. FA and SD-OCT at the time of baseline treatment decision in patient 24

a. early phase of fluorescein angiography (Topcon) showing a clear active subfoveal CNV, b. Cirrus SD-OCT (Zeiss) showing a subretinal hyperreflectivity without evident fluid.

REFERENCES

[1] Chan W-M, Ohji M, Lai TYY et al. Choroidal neovascularisation in pathological myopia: an update in management. *Br. J. Ophthalmol* 2005; 89:1522–1528.

[2] Ohno-Matsui K, Yoshida T, Futagami S et al. Patchy atrophy and lacquer cracks predispose to the development of choroidal neovascularisation in pathological myopia. *Br J Ophthalmol* 2003; 87:570–573.

[3] Green WR, Grossniklaus HE, Pathologic findings in pathologic myopia. *Retina* 1992; 12:127–133.

[4] Cohen SY, Laroche A, Leguen Y et al. Etiology of choroidal neovascularization in young patients. *Ophthalmology* 1996; 103:1241–1244.

[5] Miller DG and Singerman LJ, Natural history of choroidal neovascularization in high myopia. *Curr. Opin. Ophthalmol* 2001; 12:222–224.

[6] Bottoni F and Tilanus M, The natural history of juxtafoveal and subfoveal choroidal neovascularization in high myopia. *Int Ophthalmol* 2001; 24:249–255.

[7] Blinder KJ, Blumenkranz MS, Bressler NM et al. Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial--VIP report no. 3. *Ophthalmology* 2003; 110:667–673.

[8] Giansanti F, Virgili G, Donati MC et al. Long-term results of photodynamic therapy for subfoveal choroidal neovascularization with pathologic myopia. *Retina Phila. Pa* 2012; 32:1547–1552.

[9] Cohen SY, Salomon Y, Anti-VEGF drugs as the 2009 first-line therapy for choroidal neovascularization in pathologic myopia. *Retina Phila. Pa* 2009; 29:1062–1066.

[10] Yoon JU, Byun YJ, Koh HJ, Intravitreal anti-VEGF versus photodynamic therapy with verteporfin for treatment of myopic choroidal neovascularization. *Retina Phila. Pa* 2010; 30:418–424.

[11] Gharbiya M, Giustolisi R, Allievi F et al. Choroidal neovascularization in pathologic myopia: intravitreal ranibizumab versus bevacizumab--a randomized controlled trial. *Am. J. Ophthalmol* 2010; 149:458–464.

[12] Konstantidinis L, Mantel I, Pournaras JA et al. Intravitreal ranibizumab (Lucentis) for the treatment of myopic choroidal neovascularization. *Graefes Arch Clin Exp Ophthalmol* 2009; 247:311-318.

[13] Cha D, Kim T, Heo J et al. Comparison of 1-year therapeutic effect of ranibizumab and bevacizumab for myopic choroidal neovascularization: a retrospective, multicenter, comparative study. *BMC Ophthalmol* 2014;14:69.

[14] Tufail A, Patel PJ, Sivaprasad S et al. Ranibizumab for the treatment of choroidal neovascularisation secondary to pathological myopia: interim analysis of the REPAIR study. *Eye Lond. Engl* 2013; 27:709–715.

[15] Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: A Randomized Controlled Study of Ranibizumab in Patients with Choroidal Neovascularization Secondary to Pathologic Myopia. *Ophthalmology* 2014; 121:682–692.

[16] Franqueira N, Cachulo ML, Pires I et al. Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab. *Ophthalmol. J. Int. Ophtalmol. Int. J. Ophthalmol. Z. Für Augenheilkd* 2012; 227:39–44.

[17] Lai TYY, Luk FOJ, Lee GKY et al. Long-term outcome of intravitreal anti-vascular endothelial growth factor therapy with bevacizumab or ranibizumab as primary treatment for subfoveal myopic choroidal neovascularization. *Eye Lond. Engl* 2012; 26:1004–1011.

[18] Hefner L, Riese J, Gerding H, Three years follow-up results of ranibizumab treatment for choroidal neovascularization secondary to pathologic myopia. *Klin. Monatsblätter Für Augenheilkd* 2013; 230:401–404.

[19] Yang HS, Kim J-G, Kim JT et al. Prognostic Factors of Eyes With Naïve Subfoveal Myopic Choroidal Neovascularization After Intravitreal Bevacizumab. *Am. J. Ophthalmol* 2013;156:1201–1210.

[20] Peiretti E, Vinci M, Fossarello M, Intravitreal bevacizumab as a treatment for choroidal neovascularisation secondary to myopia: 4-year study results. *Can. J. Ophthalmol. J. Can. Ophtalmol* 2012; 47:28–33.

[21] Silva RM, Ruiz-Moreno JM, Rosa P et al. Intravitreal ranibizumab for myopic choroidal neovascularization: 12-month results. *Retina Phila. Pa* 2010; 30:407–412.

[22] Hefner L, Riese J, Gerding H, Three years follow-up results of ranibizumab treatment for choroidal neovascularization secondary to pathologic myopia. *Klin. Monatsblätter Für Augenheilkd* 2013; 230:401–404.

[23] Ruiz-Moreno JM, Arias L, Montero JA et al. Intravitreal anti-VEGF therapy for choroidal neovascularisation secondary to pathological myopia: 4-year outcome. *Br. J. Ophthalmol* 2013; 97:1447–1450.

[24] Yoshida T, Ohno-Matsui K, Yasuzumi K et al. Myopic choroidal neovascularization: a 10-year follow-up. *Ophthalmology* 2003; 110:1297–1305.

[25] Martin DF, Maguire MG, Fine SL et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration. *Ophthalmology* 2012; 119:1388–1398.

[26] Schnichels S, Hagemann U, Januschowski K et al. Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells. *Br. J. Ophthalmol* 2013; 97:917–923.

[27] Neelam K, Cheung CMG, Ohno-Matsui K et al. Choroidal neovascularization in pathological myopia. *Prog. Retin. Eye Res* 2012; 31:495–525.

[28] Campa C, Costagliola C, Incorvaia C et al. Inflammatory Mediators and Angiogenic Factors in Choroidal Neovascularization: Pathogenetic Interactions and Therapeutic Implications. *Mediators Inflamm* 2010; 2010:1–14.

[29] Dong A, Seidel C, Snell D et al. Antagonism of PDGF-BB suppresses subretinal neovascularization and enhances the effects of blocking VEGF-A. *Angiogenesis* 2014; 17:553–562.

[30] Leveziel N, Caillaux V, Bastuji-Garin S et al. Angiographic and Optical Coherence Tomography Characteristics of Recent Myopic Choroidal Neovascularization. *Am. J. Ophthalmol* 2013;155:913–919.