Year : 2016

Pigment Epithelial Detachment Response to Aflibercept in Neovascular Age-Related Macular Degeneration Refractory to Ranibizumab: Time Course and Drug Effects

de MASSOUGNES Sophie

UNIVERSITÉ DE LAUSANNE - FACULTÉ DE BIOLOGIE ET DE MÉDECINE

Service d'Ophtalmologie
Département de Rétine Médicale

Pigment Epithelial Detachment Response to Aflibercept in Neovascular Age-Related Macular Degeneration Refractory to Ranibizumab: Time Course and Drug Effects

THESE

préparée sous la direction de la Docteure Mantel

et présentée à la faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEURE EN MEDECINE

par

Sophie de MASSOUGNES

Médecin diplômée de la Confédération Suisse
Originaire de Berzona (Tessin)

Lausanne

2016

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Ecole Doctorale
Doctorat en médecine

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Directeur de thèse	*Madame la Docteure* ***Irmela Mantel***
Co-Directeur de thèse	
Expert	
Vice-Directeur de l'Ecole doctorale	*Monsieur Le Professeur* ***John Prior***

la Commission MD de l'Ecole doctorale autorise l'impression de la thèse de

Madame Sophie DE MASSOUGNES

intitulée

Pigment epithelial detachment response to aflibercept in neovascular age-related macular degeneration refractory to ranibizumab : time course and drug effects

Lausanne, le 6 décembre 2016

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

RÉSUMÉ

La dégénérescece maculaire liée à lâge (DMLA), dans sa forme sèche ou humide, est la première cause de malvoyance des pays industrialisés.

La mise sur le marché des traitements par injections intravitréennes d'anti-VEGF en 2006 a révolutionné la prise en charge des formes humides, permettant le maintien voire l'amélioration de la vision de la majorité des patients traités. Il existe toutefois des patients réfractaires au traitement. Certains phénotypes de la maladie sont également associés à un plus mauvais pronostic visuel, notamment ceux présentant un décollement de l'épithélium pigmentaire (DEP).

Une nouvelle molécule anti-VEGF, l'aflibercept, a été introduite en Suisse en 2012. Son profil d'activité est légèrement différent de celui du ranibizumab, la molécule jusqu'alors la plus fréquemment utilisée dans notre clinique. Suite à la publication dans la littérature internationale de cas de DMLA réfractaires présentant une bonne réponse à un changement de thérapie nous avons modifié le traitement d'une partie des patients de notre cohorte. Nous avons ensuite analysé rétrospectivement l'évolution de cette série de patients "switchés" du ranibizumab vers l'aflibercept, et parmi eux, ceux présentant un DEP, facteur de moins bon pronostic visuel.

Notre protocole d'étude a retenu les patients réfractaires switchés après au minimum 9 mois de traitement bien conduit par ranibizumab. Cela représente 60 yeux de 50 patients, étudiés rétrospectivement à 4 différents intervalles, 9 mois avant le changement de thérapie, au moment du changement, 3 et 9 mois après. Les critères d'analyses ont été, notamment, la meilleure acuité visuelle corrigée et la taille du DEP. Les différents intervalles d'évaluation ont permis d'établir une courbe représentant l'évolution de la taille du décollement de l'épithélium pigmentaire au cours du temps.

Il ressort de notre étude que le changement de molécule n'a pas eu de répercussion significative sur l'acuité visuelle. La petite taille de notre groupe peut être en cause, ne permettant pas de déceler de petits changements, de même que la longue durée de traitement avant le switch, en moyenne 3 ans, avec des atteintes de la fonction irréversibles.

Concernant l'anatomie, la taille du DEP a progressivement diminué, que ce soit sous un traitement par ranibizumab ou par aflibercept. La pente de la courbe a accéléré significativement dans les 3 mois suivant le changement de thérapie. Nous avons pu mettre en évidence que certains patients "très bons répondeurs" ont influencé ce résultat.

En conclusion, selon nos résultats, le changement de thérapie de ranibizumab à aflibercept chez des patients réfractaires présentant un DEP n'influence pas le pronostic visuel. Le DEP diminue continuellement de taille sous traitement. Certains patients "bons répondeurs" présentent après le changement de molécule une accéleration de la réduction de taille, voire parfois la résolution du DEP toutefois sans répercussion notable sur l'acuité visuelle.

Ce résultat encourage à davantage d'études longitudinales et comparatives afin de mieux comprendre le rôle des différentes molécules de traitement et mieux comprendre les différents phénotypes des patients, vers une personnalisation précoce des prises en charge.

Pigment Epithelial Detachment Response to Aflibercept in Neovascular Age-Related Macular Degeneration Refractory to Ranibizumab: Time Course and Drug Effects

Abbreviated title: Aflibercept for refractory nAMD and PED

Sophie de Massougnes, MD[1]

Ali Dirani, MD[1]

Aude Ambresin, MD[1]

Doris Decugis[1]

Laetitia Marchionno[1]

Irmela Mantel, MD[1]

[1] Department of Ophthalmology, University of Lausanne, Jules Gonin Eye Hospital, Fondation Asile des Aveugles, Lausanne, Switzerland

Correspondence and reprint requests to: Irmela Mantel, MD, Jules Gonin Eye Hospital, 15 Avenue de France, Case postale 133, CH-1000, Lausanne 7, Switzerland. Tel: +41-21-626 85 89; fax: +41-21-626 88 88; e-mail: irmela.mantel@fa2.ch.

Presentation at meetings: The results of this study have been presented in parts at the Euretina congress, London 2014

Funding: none

Conflict of interest: none

Key words: angiogenesis, antiangiogenic drugs, intravitreal injection, retinal pigment epithelial detachment, vascular endothelial growth factor, visual impairment, neovascular age-related macular degeneration, ranibizumab, aflibercept, refractoriness

Summary: In patients with neovascular age-related macular degeneration refractory to ranibizumab, an associated pigment epithelium detachment slowly decreased in height. Switching to aflibercept resulted in a steeper short term decrease of retinal pigment epithelial detachment height. Visual acuity remained stable.

Abstract

Purpose: To investigate the time course of pigment epithelium detachment (PED) height, and its change after anti-VEGF switch from ranibizumab to aflibercept in neovascular age-related macular degeneration (nAMD).

Methods: This retrospective study included 60 eyes of 50 consecutive patients with nAMD who showed refractory intra- or subretinal fluid (≥9 months) despite monthly ranibizumab treatment, and an associated PED (height ≥150 μm). The treatment was switched to aflibercept, and patients were followed up for at least 9 months. Data on the height and type of PED, exudative fluid, and best-corrected visual acuity were collected at four different time points (two before, and two after the drug switch).

Results: The maximal PED height was significantly decreased over time, both under ranibizumab and aflibercept treatment. However, the reduction was significantly greater during the 3 months following the switch to aflibercept, due to two outliers. Visual acuity remained stable. Complete resolution of intra- or subretinal fluid was observed in 9 cases (15%) at 3 months after switch, allowing for treatment interval extension.

Conclusion: Maximal PED height continuously decreased over time. Switching the intravitreal anti-VEGF medication from ranibizumab to aflibercept had a significantly stronger short-term effect on PED height reduction, without changes in visual acuity.

Introduction

Neovascular age-related macular degeneration (nAMD) is a frequent and sight-threatening disorder of the elderly. Treatment with intravitreal anti-vascular endothelial growth factor (VEGF) injections has been shown to effectively improve visual acuity outcomes in nAMD, both with ranibizumab[1,2] and aflibercept.[3,4] Ranibizumab is a humanized monoclonal antibody antigen-binding fragment, which inhibits all biologically active isoforms of VEGF-A. This molecule was approved for treatment of nAMD and became commercially available in 2006. Aflibercept is a recombinant fusion protein of components of VEGF receptor (VEGFR) 1 and 2. It antagonizes not only VEGF-A but also VEGF-B and placental growth factor (PlGF).[5] Aflibercept became FDA-approved in 2011 and available in Switzerland in 2012. VIEW 1 and VIEW 2 trials demonstrated equally good efficacy of the two drugs in terms of visual acuity and anatomic outcomes.[3] The number of retreatments in the pro re nata period (second year) was lower for the 2mg dose of aflibercept.[4] Pharmacological studies comparing ranibizumab and aflibercept have shown that aflibercept has a higher binding affinity to VEGF-A[5] and a theoretically longer ligand-binding activity.[6] These differences have led to several studies on the advantages of switching from ranibizumab and/or bevacizumab to aflibercept in cases of refractory or rapidly recurrent fluid in nAMD. Those studies showed improved anatomical[7-20] but usually no functional benefit with the exception of few studies.[18-20] No difference in efficacy was found in the pivotal trials, and the reasons for this contrast are not yet fully understood. It is possible that particular subgroups have different responses, and that time plays an important role.

The aim of this study was to analyze a particular subgroup of patients with nAMD, characterized by the presence of pigment epithelium detachment (PED), and to

evaluate their response to a switch from ranibizumab to aflibercept. As the natural course of PED also includes a trend towards flattening after initial progression,[21] we attempted in this study to distinguish the effect of time from the effect of the drug switch by including four different time points in the analysis: two before, and two after the drug switch.

Methods

This retrospective study was performed at the Medical Retina Service of the tertiary referral center Jules Gonin University Eye Hospital in Lausanne, Switzerland. The study was approved by the Swiss Federal Department of Health for retrospective data analysis, and was performed in accordance with the ethical standards in the Declaration of Helsinki.

The local database was used to systematically identify all consecutive nAMD patients with refractoriness to ranibizumab treatment during at least 9 months (defined as the presence of intra- or subretinal fluid at each visit one month after injection), leading to treatment switch from ranibizumab to aflibercept between December 2012 and September 2013. Of these, only those with a PED of at least 150 μm in height on spectral domain optical coherence tomography (SD-OCT) at the time point of switch were included in the analysis.

The treatment regimen varied between a pro re nata (before March 2010) and treat-and-extend regimen (from March 2010 onwards). Despite the variable dosing regimen, refractoriness led to monthly retreatment during at least 9 months before switching to aflibercept. The retreatment criterion was intra- and/or subretinal fluid on SD-OCT, but not fluid immediately underneath the PED. When changing to aflibercept because of refractoriness, the eye was treated with three monthly

aflibercept intravitreal injections before the treatment interval was extended in case of absence of intra- and suretinal fluid.

Exclusion criteria were: PED height <150 μm on SD-OCT at the time of treatment switch; polypoidal choroidal vasculopathy (most of them were treated with combined anti-VEGF and photodynamic therapy), or any confounding retinal pathology such as diabetic maculopathy or pathologic myopia; insufficient fundus image quality; and patients undergoing any combination therapy.

Baseline examination and all subsequent follow-up visits included best-corrected visual acuity (BCVA) on Early Treatment of Diabetic Retinopathy (ETDRS) chart, a slit lamp examination, measurement of the intraocular pressure (IOP), a dilated fundus exam, and an OCT examination (128 × 512 cube examination on SD-OCT Cirrus [Carl Zeiss Meditec, Inc., Oberkochen, Germany] from January 2009; 49 line cube examination on Spectralis [Heidelberg Engineering, Heidelberg, Germany] from March 2012). Fundus color photography, fundus autofluorescence (FAF) imaging, fluorescein angiography (FA), and indocyanine green angiography (ICGA) (Topcon TRC-501X; Tokyo, Japan) were performed at baseline, at month 3, and then annually. Additional imaging was performed at the physician's discretion.

Data were collected for age, gender, laterality, follow-up duration before and after the switch, number of injections, angiographic lesion type, and the presence of PED at baseline and at the time of treatment switch. The degree of PED vascularization was categorized according to the ICGA into predominantly serous if less than 50% of the lesion was vascularized, or predominantly vascularized if 50% or more of the lesion was vascularized. In addition, the following data were recorded for four different time points (9 months before treatment switch [M-9], at the time of the switch [M0], and 3 and 9 months later [M3 and M9, respectively]): PED height

subfoveal and at the highest point (measured from underneath the hyperreflective pigment epithelium band perpendicular to Bruch's Membrane on SD-OCT on a 1:1 μm scale); the central retinal thickness as measured on Spectralis SD-OCT; and the presence or absence of intra- or subretinal fluid.

The statistical analysis was performed as paired comparisons between these time points, and for the rate of change between the time points. For data analysis, a spreadsheet on Microsoft Excel 2010 and SPSS for Windows (version 17.0; SPSS, Inc.; Chicago, IL) were used. The paired *t*-test and Wilcoxon test were used for comparison between paired continuous variables, and *t*-test and Mann–Whitney test were used for comparison between subgroups. Statistical significance was set at $p < 0.05$.

Results

During the study period, 116 eyes of 108 patients were switched from ranibizumab to aflibercept. Of these, 48 eyes were excluded as they presented no PED or PED <150 μm at the time of the switch, and 8 eyes were excluded because of loss to follow-up after the switch. Finally, 60 eyes of 50 patients were included.

The demographic, angiographic, OCT, and treatment characteristics of all included study patients are summarized in Table 1. The average age of patients (± standard deviation [SD]) was 79 ± 7.1 years. Thirty-three patients (66.6%) were female. Before treatment switch, patients had been followed up for a mean of 35.7 ± 18.1 months and had undergone a mean of 26.1 ± 12.0 ranibizumab injections. During the year preceding the treatment switch, a mean of 10.0 ± 1.4 injections had been given. Intraretinal refractory fluid (cysts) was present in 25 eyes (41.7%), and subretinal refractory fluid in 47 eyes (78.3%). Most eyes (68.3%) had occult choroidal

neovascularization, and the PED was predominantly vascularized in 46 eyes (76.7%).

The mean PED height at its highest elevation point (maximum PED height) decreased continuously at each time point of the study, from 340 ± 165 μm at M-9, to 313 ± 131 μm, 277 ± 125 μm, and 275 ± 123 μm at M0, M3, and M9, respectively (Figure 1a). The mean maximum PED height tended to be lower at M0 than at M-9 ($p = 0.079$), and was significantly lower at M3 than at M0 ($p = 0.004$). The mean / median change per month (slope of the time-adjusted line) of the highest PED height was -2.93 / -0.39 from M-9 to M0, -11.87 / -4.83 from M0 to M3, and -0.49 / -0.58 from M3 to M9. This was significantly steeper during the 3 months following the switch as compared to the 9 months prior to the switch ($p = 0.047$) and the 6 following months ($p = 0.011$). However, the mean change per month was not significantly different when comparing the nine month periods prior to and after the drug switch ($p = 0.54$) (Figure 1a).

Foveal involvement in the PED was seen in 56 out of the 60 eyes (93%). The PED height underneath the central foveal point showed a similar pattern of regression over time (Figure 1b) with a mean height of 203 ± 187 μm, 178 ± 137 μm, 162 ± 139 μm, and 162 ± 138 μm at M-9, M0, M3, and M9, respectively. The subfoveal PED height tended to be lower at M0 than at M-9 ($p = 0.071$), and it was significantly lower at M3 than at M0 ($p < 0.001$). The mean change per month was not significantly different in the nine months periods prior to and after the drug switch ($p = 0.477$). However, there was a non-significant acceleration of height reduction within the 3 first months after the switch ($p = 0.15$), after which height reduction slowed down.

During the period from M0 to M3, only 2 eyes (3%) showed more than 150 μm reduction of the highest PED elevation. Their relative PED height reduction was 82% and 71%, respectively; they were the only patients with a relative height reduction of more than 50%. A PED height reduction of 30% and 20% or more was achieved in 7 (12%) and 15 (25%) eyes, respectively. However, most eyes (75%) had less than 20% height reduction. The two patients with the strongest PED flattening (proportional height reduction) from M0 to M3 were clear statistical outliners. Therefore, the main analysis was repeated after excluding them. The results changed in the following way: While the comparison between the time points still revealed a similar pattern of continuous change of the PED height over time (M-9 versus M0, $p = 0.064$; M0 versus M3, $p < 0.001$), the mean change per month was not significantly different between M-9–M0 and M0–M3 ($p = 0.14$). Thus, it appeared that the 2 outliner cases were responsible for the significant short term acceleration (slope) of PED height reduction after the drug switch.

Central retinal thickness was available on the Spectralis SD-OCT from M0 only. The results showed a significant decrease from 372 ± 111 μm at M0 to 321 ± 92 μm at M3 ($p < 0.001$). However, no further regression was observed between M3 and M9 ($p = 0.66$). The slope of the curve was marginally different between the first 3 months after the switch and the period between M3 and M9 ($p = 0.092$) (Figure 2a).

Both intraretinal and subretinal fluid showed similar response to medication switch: in 5/26 eyes (19%) with refractory intraretinal cysts, and in 8/48 eyes (17%) with refractory subretinal fluid, there was resolution of fluid at M3. Eight out of the 60 included eyes (13%) with any refractory fluid were judged completely dry at M3, and this proportion increased to 10 (17%) at M9.

In comparison with the eyes with incomplete fluid resolution, the 8 eyes with complete fluid resolution at M3 showed significantly greater PED height reduction at M3 ($p = 0.009$) (Figure 3a). Those 8 eyes had greater PED at M-9 ($p = 0.05$), showed stronger height reduction under ranibizumab during M-9–M0 ($p = 0.06$), resulting in similar PED height at M0 ($p = 0.70$), followed by greater PED height reduction from M0 to M3 after drug switch to aflibercept ($p = 0.001$), resulting in a PED height that was significantly lower at M3 ($p = 0.009$), a difference which was maintained at M9 ($p = 0.02$).

The subgroup analysis of predominantly serous and predominantly vascularized PED showed significantly greater PED in the predominantly serous group ($p = 0.01$) at M-9. However, the response to medication switch was not statistically different between the two subgroups (Figure 3b).

The mean BCVA was 73 ± 12 letters on the ETDRS chart at M-9, and 74 ± 12, 74 ± 12, and 74 ± 11 letters at M0, M3, and M9, respectively (no statistically significant differences) (Figure 2b).

Discussion

The results of the present study revealed two different aspects of PED evolution under anti-VEGF treatment and over time. First, there was an overall reduction of PED height over time, both at the highest PED elevation and underneath the fovea. This was well visible under ranibizumab treatment, yet only marginally significant between M9 and M0. Second, the change over time (the slope) was significantly steeper after the switch from ranibizumab to aflibercept (M0 to M3), at least in the early phase (until M3). However, with the continuation of the aflibercept treatment (M3 to M9), this initial acceleration of PED reduction was lost, and at M9 the PED

height corresponded again to what could have been expected according to the initial slow decrease under ranibizumab.

The natural course of PED, being serous or vascularized, shows an initial enlargement over months, followed by a slow decrease in size,[21] and finally resolution with remnant atrophy after years. As anti-VEGF treatment is known to have only partial effect on PED in the early course of treatment,[22,23] we may expect that the same natural course of slow decrease may be found in the chronic phase of anti-VEGF treatment. In fact, in our study cohort of refractory nAMD (in terms of persistent intra- and/or subretinal fluid), we noted such slow reduction, as documented during the 9 months of ranibizumab preceding the medication switch to aflibercept. The very long mean treatment duration of 35.7 months before medication switch in our cohort corresponds with the time period in which a slow PED flattening can be expected in the natural course.[21]

This natural history of PED makes the evaluation of the effect of the treatment more challenging. Previous studies have reported the results of medication switch from ranibizumab and/or bevacizumab to aflibercept in refractory nAMD by comparing the situation at the time of switch to a single later time point.[7-20] However, without a control group, the possible conclusions remain limited.

Grewal et al reported about the switch results in a group of nAMD patients, mostly with associated PED (71%)[12] Their results are similar to our results, as they found a significant change of the maximal PED height and central retinal thickness as compared with the time of switch and 6 and 12 months later, while BCVA showed no change.[12] A recent study by Broadhead et al reported the outcome of a PED group which underwent medication switch for refractoriness.[16] They found that PED showed

in all 3 dimensions a good response to medication switch to aflibercept, not correlated with the visual acuity change.[16]

Ideally, the effect of medication switch should be examined in comparison with a balanced control group without switch. Such a control group is difficult to establish because of various confounding factors such as previous treatment characteristics and lesion characteristics. The ideal setting for such a comparative study would be the end a prospective trial or case series.

In this study, we chose an alternative approach to separate the effect of time from the medication effect: the switch effect was analyzed within a larger time period, including four time points of measurement (two time points before the switch and two time points after the switch). Theoretically, and assuming a linear evolution of the time-dependent variable, any significant change of the slope of the curve would then express an additional effect by another factor, in this case the medication switch.

In fact, the results of our study showed an additional effect of the medication switch in terms of a significantly steeper change per time (slope) of the highest PED elevation after the switch as compared to prior the switch. This difference was statistically significant for the highest PED elevation, but not for the subfoveal location. Although switching the medication to aflibercept had a measurable effect on the PED height, this effect was a short term effect and was lost at 9 months after switch. In addition, we found that the steeper change per time was driven by two eyes that were statistical outliners. While 75% of eyes had a relative PED height change of 20% or less, only 2 eyes (3%) showed more than 50% relative height reduction. These 2 eyes with strong PED flattening after switch to aflibercept resemble the observation of Patel et al who reported a dramatic decrease of PED height in 3 patients following the switch from ranibizumab to aflibercept.[10] The two

exceptional cases in our study were in fact responsible for the significant difference between the PED height change before versus after the medication switch, as this comparison lost its statistical significance after excluding them as outliners. We may therefore suggest that the additional treatment effect of aflibercept as compared to ranibizumab may be limited to few cases.

The following potential explanations may be considered for this slightly stronger effect of aflibercept after long-term use of ranibizumab: first, the pharmacologic differences between the molecules; second, the different behavior of the drugs in the retinal tissue; and third, the phenomenon of tachyphylaxis or tolerance.

In terms of pharmacologic characteristics of aflibercept, the high affinity to its ligand VEGF-A theoretically results in a longer duration of action.[5,6] This may lead to a more pronounced effect after identical time. Perhaps more important is the different spectrum of antagonism, which includes VEGF-B and PlGF in the case of aflibercept.[5] PlGF is produced during ischemia, inflammation, and wound healing.[24] It stimulates the VEGF production,[25] and has been identified in the choroidal neovascularization process.[26] Although the role of each player within the VEGF family (which includes PlGF) is not fully understood, it is conceivable that their relative roles vary in different nAMD phenotypes. It is interesting to note that the expression of VEGFR-1 and VEGFR-2 has been shown to differ in various pathologic situations.[27-29] Furthermore, VEGF secretion has been described as polarized, with a gradient toward the choriocapillaris, where VEGF receptors were identified.[30] This polarized secretion was more pronounced under ischemic conditions.[30]

Recent fundamental research has shown a different behavior of aflibercept and ranbizumab in the retinal tissue of healthy monkeys: While ranibizumab was found in the intercellular space, aflibercept was documented intracellular to ganglion cells,

inner and outer retinal cells, and also retinal pigment epithelium cells.[31] Aflibercept caused hypertrophy and death of individual pigment epithelium cells, associated with more frequent stasis and hemolysis in the choriocapillaris.[31] It is unknown to what degree these differences play a role in human eyes. However, considering that the pigment epithelium cells are suffering due to nAMD and chronic PED, such additional toxic effect by the drug may accelerate the decompensation, leading to a decreased pumping function, and therefore flattening of the PED. Interestingly, one of our subgroup analysis showed a more pronounced PED height reduction in predominantly serous PEDs, although this did not reach statistical significance. In serous PED, the fluid underneath the retinal pigment epithelium is believed to come from the outward movement of ions and material by the retinal pigment epithelium, impaired by the thickened Bruch's membrane.[21,32] In vascularized cases it is believed to be linked to a neovascularized membrane underneath the pigment epithelium.[21] Thus a potentially toxic effect of aflibercept on the pump function of the pigment epithelium cells would have a more pronounced effect on the PED height in serous PED, as it is related to the pump function. Furthermore, serous PED may have a higher mechanical potential for PED flattening than a vascularized PED with underlying neovascular mass lesion. Correspondingly, a recent study reported a significantly stronger reduction of PED height and extension after medication switch to aflibercept in those with hollow and mixed PED, compared with solid PED.[16] Our study found a similar difference, but not significant.

However, the selection of refractory fluid despite monthly retreatment with ranibizumab may have included a number of cases with tachyphylaxis (or tolerance) to ranibizumab.[33-35] A pharmacodynamic tolerance could correspond to the increased synthesis of VEGF and/or VEGFR molecules.[36] Another possible mechanism would

be a pharmacokinetic tolerance secondary to the development of neutralizing antibodies. Immunoreactivity in the serum has been demonstrated in 8.2% of patients after 24 months of treatment with 0.5 mg ranibizumab in the ANCHOR study.[1] Several authors have postulated tolerance or tachyphylaxis in order to explain the reduced efficacy of anti-VEGF treatment over time.[14,34,37] With the assumption of immunologic neutralization of the anti-VEGF, any change to an immunologically different molecule could be expected to show increased efficacy, in a way comparable with the effect of the initial loading phase.[22] The observation of absence of further effect after the three aflibercept doses would also correspond with such analogy to the initial loading doses. Interestingly, there was a statistically significant stronger PED height reduction in those patients, who also showed complete absorption of the refractory intra- and subretinal fluid. Such successful response in all three retinal compartments (intra-, sub-retinal, and sub-retinal pigment epithelium) supports the “tolerance” hypothesis to previous ranibizumab.

In our study, only 13% of the eyes showed complete dryness of the macula at 3 months and benefited from an extension of the retreatment interval. This proportion is lower than that in other reports after switch to aflibercept,[3,4,11] possibly due to the PED, which is known to induce a poor response.[38,39] In the present study, it was not possible to identify to what degree this response was related to the medication switch, as time might as well induce resolution of fluid despite previous refractoriness.[40]

Despite a change in maximal size of PED we did not record any significant change of BCVA, similar to most previous switch reports in neovascular AMD. Our cohort may be too small to detect small modifications. However, chronicity of the disease (mean time to treatment switch almost 3 years) might preclude any visual

benefit due to structural damage. Neovascular AMD with PED is known for poor long-term visual acuity prognosis.[21,39,41] However, the functional importance of therapeutically flattening the PED is unknown.

This study has several limitations. Besides the inherent weaknesses of a retrospective study design, we need to acknowledge the lack of reliable CRT data nine months before switch due to the use of different OCT machines. Additional weaknesses are the manual measurement of the PED height data, and the lack of a control group.

In conclusion, the present study demonstrated that the PED height continuously regressed over time in cases of nAMD under chronic treatment with anti-VEGF. The medication switch from ranibizumab to aflibercept, which was motivated by the associated refractory sub- or intraretinal fluid, induced an additional, short-term PED height reduction of limited extent in the initial phase of aflibercept. The functional importance of this height reduction is unclear: BCVA did not show any significant change during the study period, and the potential reasons for the stronger aflibercept effect include not only a more pronounced therapeutic effect but also the possibility of toxicity to the pigment epithelium. This analysis contributes to the discussion of the differences between the molecules aflibercept and ranibizumab. It also highlights that longitudinal interventional studies show both the effect of the intervention and the underlying evolution over time. Therefore, comparative studies are needed to better understand the role of different molecules in treating nAMD with PED.

References

1. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study. *Ophthalmology* 2009;116(1):57–65.

2. Rosenfeld PJ, Brown DM, Heier JS. Ranibizumab for Neovascular Age-Related Macular Degeneration. *N Engl J Med* 2006; 355(14):1419-31.

3. Heier JS, Brown DM, Chong V, et al. Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration. *Ophthalmology* 2012;119(12):2537–2548.

4. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration. *Ophthalmology.* 2014;121(1):193–201.

5. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis*. 2012;15(2):171–185.

6. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol* 2008;92(5):667–668.

7. Bakall B, Folk JC, Boldt HC, et al. Aflibercept Therapy for Exudative Age-related Macular Degeneration Resistant to Bevacizumab and Ranibizumab. *Am J Ophthalmol*. 2013;156(1):15–22.

8. Cho H, Shah CP, Weber M, et al. Aflibercept for exudative AMD with persistent fluid on ranibizumab and/or bevacizumab. *Br J Ophthalmol*. 2013;97(8):1032–1035.

9. Ho VY, Yeh S, Olsen TW, et al. Short-Term Outcomes of Aflibercept for Neovascular Age-Related Macular Degeneration in Eyes Previously Treated With Other Vascular EndothelialGrowth Factor Inhibitors. *Am J Ophthalmol*. 2013;156(1):23–28.

10. Patel KH, Chow CC, Rathod R, et al. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. *Eye* 2013;27(5): 663–668.

11. Yonekawa Y, Andreoli C, Miller JB, et al. Conversion to Aflibercept For Chronic Refractory Or Recurrent Neovascular Age-Related Macular Degeneration. *Am J Ophthalmol*. 2013;156(1):29–35.

12. Grewal DS, Gill MK, Sarezky D, et al. Visual and anatomical outcomes following intravitreal aflibercept in eyes with recalcitrant neovascular age-related macular degeneration: 12-month results. *Eye* 2014;28(7):895–899.

13. Heussen FM, Shao Q, Ouyang Y, Joussen AM, Müller B. Clinical outcomes after switching treatment from intravitreal ranibizumab to aflibercept in neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2013;252(6):909–915.

14. Wykoff CC, Brown DM, Maldonado ME, Croft DE. Aflibercept treatment for patients with exudative age-related macular degeneration who were incomplete responders to multiple ranibizumab injections (TURF trial). *Br J Ophthalmol*. 2014;98(7):951–955.

15. Gharbiya M, Iannetti L, Parisi F, De Vico U, Mungo ML, Marenco M. Visual and

Anatomical Outcomes of Intravitreal Aflibercept for Treatment-Resistant Neovascular Age-Related Macular Degeneration. *BioMed Research International*. 2014;2014(12):813–825.

16. Broadhead GK, Hong T, Zhu M, et al. Response of pigment epithelial detachments to intravitreal aflibercept among patients with treatment-resistant neovascular age-related macular degeneration. *Retina.* 2015;35(5):975–981.

17. Arcinue CA, Ma F, Barteselli G, et al. One-Year Outcomes of Aflibercept in Recurrent or Persistent Neovascular Age-Related Macular Degeneration. *Am J Ophthalmol*. 2015;159(3):426–436.

18. Chang AA, Li H, Broadhead GK, et al. Intravitreal Aflibercept for Treatment-Resistant Neovascular Age-related Macular Degeneration. *Ophthalmology.* 2014;121(1):188–192.

19. Kumar N, Marsiglia M, Mrejen S, et al. Visual and anatomical outcomes of intravitreal aflibercept in eyes with persistent subfoveal fluid despite previous treatments with ranibizumab in patients with neovascular age-related macular degeneration. *Retina*. 2013;33(8):1605–1612.

20. Hariri A, Diniz B, Fou LV, et al. Quantitative OCT Subanalysis of Eyes With Choroidal Neovascularization Switched From Multiple Injections of Bevacizumab or Ranibizumab to Intravitreal Aflibercept. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46(2):195–200.

21. Pauleikhoff D, Löffert D, Spital G, et al. Pigment epithelial detachment in the elderly. Clinical differentiation, natural course and pathogenetic implications. *Graefes Arch Clin Exp Ophthalmol*. 2002;240(7):533–538.

22. Punjabi OS, Huang J, Rodriguez L et al. Imaging characteristics of neovascular pigment epithelial detachments and their response to anti-vascular endothelial growth factor therapy. *Br J Ophthalmol*. 2013;97(8):1024–1031.

23. Wolf A, Rüping J, Neubauer AS, et al. Alterations of vascular pigment epithelium detachments associated with age-related macular degeneration during upload with intravitreal ranibizumab. *Retina.* 2013;33(9):1843–1849.

24. Carmeliet P, Moons L, Luttun A, et al. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. *Nat Med*. 2001;7(5):575–583.

25. Bottomley MJ, Webb NJA, Watson CJ, et al. Placenta growth factor (PlGF) induces vascular endothelial growth factor (VEGF) secretion from mononuclear cells and is co-expressed with VEGF in synovial fluid. *Clin Exp Immunol*. 2000;119(1):182–188.

26. Rakic J-M, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. *Invest Ophthalmol Vis Sci*. 2003;44(7):3186–3193.

27. Witmer AN, Blaauwgeers HG, Weich HA, et al. Altered expression patterns of VEGF receptors in human diabetic retina and in experimental VEGF-induced retinopathy in monkey. *Invest Ophthalmol Vis Sci*. 2002;43(3):849–857.

28. Ozaki NK, Beharry KD, Nishihara KC, et al. Regulation of retinal vascular endothelial growth factor and receptors in rabbits exposed to hyperoxia. *Invest Ophthalmol Vis Sci*. 2002;43(5):1546–1557.

29. Wada M, Ogata N, Otsuji T, Uyama M. Expression of vascular endothelial growth factor and its receptor (KDR/flk-1) mRNA in experimental choroidal neovascularization. *Curr Eye Res*. 1999;18(3):203–213.

30. Blaauwgeers HG, Holtkamp GM, Rutten H, et al. Polarized vascular endothelial growth factor secretion by human retinal pigment epithelium and localization of vascular endothelial growth factor receptors on the inner choriocapillaris. Evidence for a trophic paracrine relation. *Am J Pathol*. 1999;155(2):421–428.

31. Julien S, Biesemeier A, Taubitz T, Schraermeyer U. Different effects of intravitreally injected ranibizumab and aflibercept on retinal and choroidal tissues of monkey eyes. *Br J Ophthalmol*. 2014;98(6):813–825.

32. Holz FG, Sheraidah G, Pauleikhoff D, Bird AC. Analysis of lipid deposits extracted from human macular and peripheral Bruch's membrane. *Arch Ophthalmol*. 1994;112(3):402–406.

33. Keane PA, Liakopoulos S, Ongchin SC, et al. Quantitative Subanalysis of Optical Coherence Tomography after Treatment with Ranibizumab for Neovascular Age-Related Macular Degeneration. *Invest Ophthalmol Vis Sci*. 2008;49(7):3115–3120.

34. Gasperini JL, Fawzi AA, Khondkaryan A, et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. *Br J Ophthalmol*. 2011;96(1):14–20.

35. Schaal S, Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? *Ophthalmology.* 2008;115(12):2199–2205.

36. Binder S. Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance? *Br J Ophthalmol*. 2011;96(1):1–2.

37. Eghoj MS, Sorensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. *Br J Ophthalmol*. 2011;96(1):21–23.

38. Guber J, Josifova T, Henrich PB, Guber I. Clinical Risk Factors for Poor Anatomic Response to Ranibizumab in Neovascular Age-Related Macular Degeneration. *Open Ophthalmol J*. 2014;8:3–6.

39. Mariani A, Deli A, Ambresin A, Mantel I. Characteristics of eyes with secondary loss of visual acuity receiving variable dosing ranibizumab for neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(11):1635–1642.

40. Jang L, Gianniou C, Ambresin A, Mantel I. Refractory subretinal fluid in patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab: visual acuity outcome. *Graefes Arch Clin Exp Ophthalmol*. 2014.

41. Hoerster R, Muether PS, Sitnilska V, Kirchhof B, Fauser S. Fibrovascular pigment epithelial detachment is a risk factor for long-term visual decay in neovascular age-related macular degeneretion. *Retina* 2014; 34(9):1767-73.

Figure legends

Figure 1:

Title:

Pigment epithelium detachment height in age-related macular degeneration refractory to ranibizumab: evolution of the mean pigment epithelium detachment height (a) at the point of the highest elevation and (b) at the subfoveal location, before and after medication switch.

Legend:

M-9= 9 months before switching from ranibizumab to aflibercept; M0= time of switch from ranibizumab to aflibercept; M3= 3 months after switch; M9= 9 months after switch; PED= pigment epithelium detachment. Error bars represent the standard deviation.

Figure 2:

Title:

Central retinal thickness and best-corrected visual acuity in age-related macular degeneration refractory to ranibizumab: evolution after medication switch.

Legend:

ETDRS= Early Treatment Diabetic Retinopathy Study scale for visual acuity; M-9= 9 months before switching from ranibizumab to aflibercept; M0= time of switch from ranibizumab to aflibercept; M3= 3 months after switch; M9= 9 months after switch; Error bars represent the standard deviation

Figure 3:

Title:

Subgroup analysis of the pigment epithelium detachment height evolution (highest elevation point) according to (a) complete or incomplete resolution of intra- and/or subretinal fluid 3 months after medication switch from ranibizumab to aflibercept and (b) the degree of vascularization on indocyanine green angiography.

Legend:

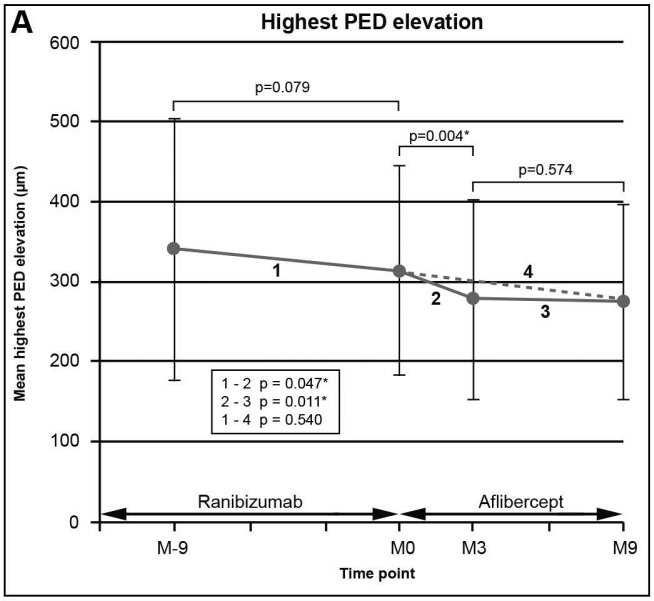
M-9= 9 months before switching from ranibizumab to aflibercept; M0= time of switch from ranibizumab to aflibercept; M3= 3 months after the switch; M9= 9 months after the switch; PED= pigment epithelium detachment. Error bars represent the standard deviation; predominantly serious = less than 50% vascularized on indocyanine green angiography; predominantly vascularized = more than 50% vascularized on indocyanine green angiography

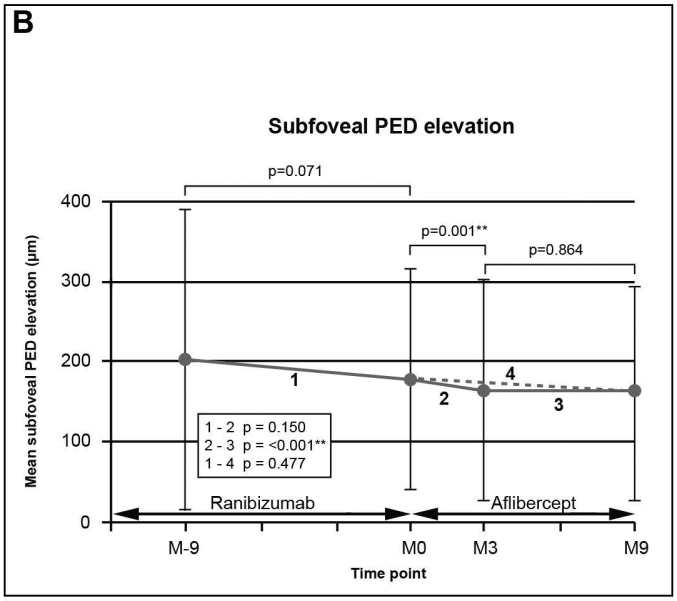
Table 1

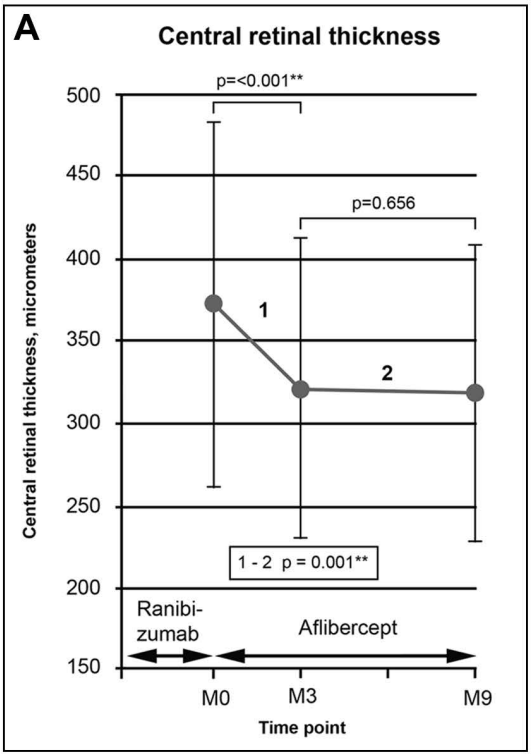
Demographic, angiographic, OCT, and treatment characteristics of all included study patients.

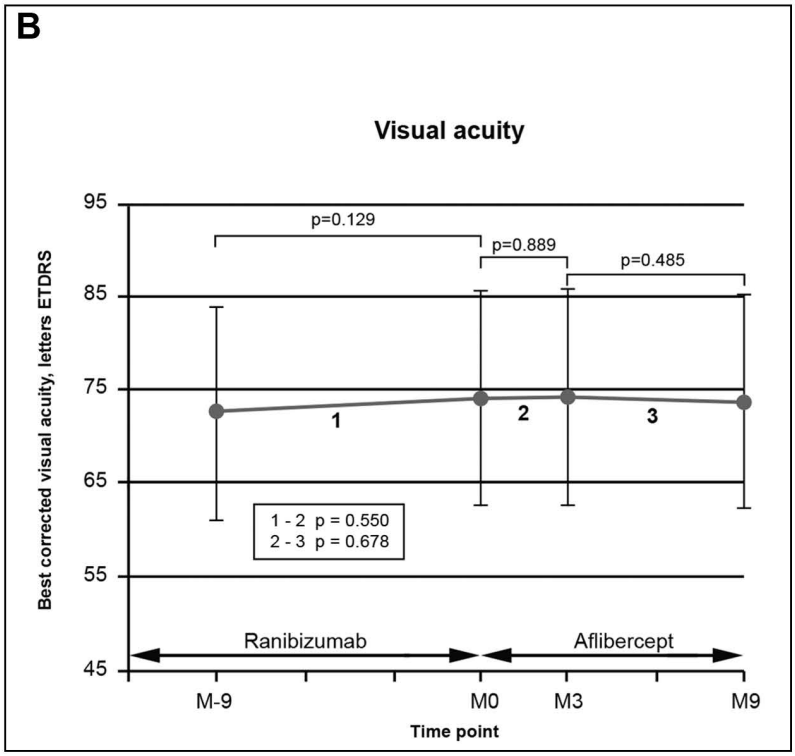
N eyes (N patients)	60 (51)
Mean age (SD), years	78.8 (7.1)
Gender distribution, female/male	33/17 (66%/34%)
Mean follow-up (SD) prior to switch, months	35.7 (18.1)
Mean number of ranibizumab injections (SD) prior to switch	26.1 (12.0)
Refractory fluid on OCT	
Intraretinal	25 (41.7%)
Subretinal	47 (78.3%)
Angiographic type of CNV	
Predominantly classic	5 (8.3%)
Minimally classic	9 (15.0%)
Occult	41 (68.3%)
RAP	5 (8.3%)
Angiographic type of PED	
Predominantly serous	14 (23.3%)
Predominantly vascularized	46 (76.7%)
Mean PED height (SD), μm	
At the highest point	313 (131)
Subfoveal elevation	178 (137)

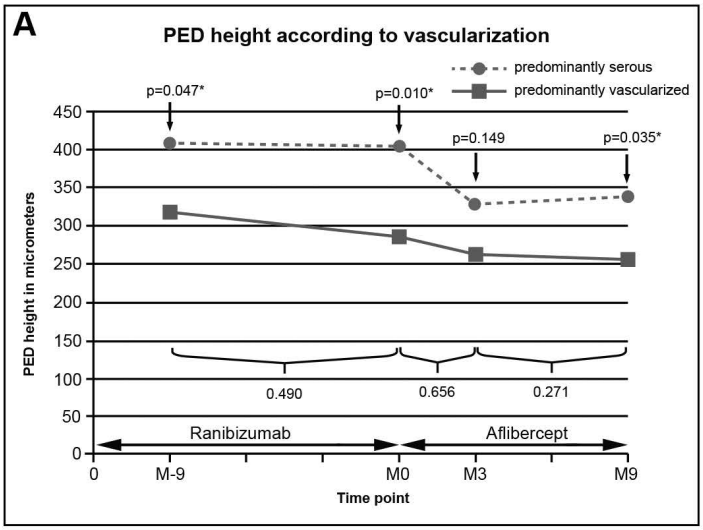
CNV, choroidal neovascularization; OCT, optical coherence tomography; PED, pigment epithelium detachment; RAP, retinal angiomatous proliferation; SD, standard deviation

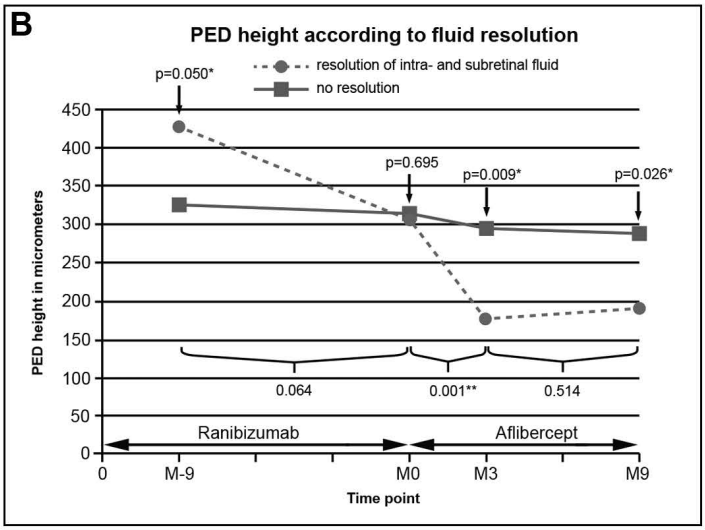

A
Highest PED elevation
Mean highest PED elevation (µm)
600
500
400
300
200
100
0
p=0.079
p=0.004*
p=0.574
1
2
3
4
1 - 2 p = 0.047*
2 - 3 p = 0.011*
1 - 4 p = 0.540
Ranibizumab
Aflibercept
M-9
M0
M3
M9
Time point


B
Subfoveal PED elevation
Mean subfoveal PED elevation (µm)
400
300
200
100
0
p=0.071
p=0.001**
p=0.864
1
2
3
4
1 - 2 p = 0.150
2 - 3 p = <0.001**
1 - 4 p = 0.477
Ranibizumab
Aflibercept
M-9
M0
M3
M9
Time point


A
Central retinal thickness
Central retinal thickness, micrometers
500
450
400
350
300
250
200
150
p=<0.001**
p=0.656
1
2
1 - 2 p = 0.001**
Ranibi-
zumab
Aflibercept
M0
M3
M9
Time point


B
Visual acuity
Best corrected visual acuity, letters ETDRS
95
85
75
65
55
45
p=0.129
p=0.889
p=0.485
1
2
3
1 - 2 p = 0.550
2 - 3 p = 0.678
Ranibizumab
Aflibercept
M-9
M0
M3
M9
Time point


A
PED height according to vascularization
predominantly serous
predominantly vascularized
p=0.047*
p=0.010*
p=0.149
p=0.035*
PED height in micrometers
450
400
350
300
250
200
150
100
50
0
0.490
0.656
0.271
Ranibizumab
Aflibercept
0
M-9
M0
M3
M9
Time point


B
PED height according to fluid resolution
resolution of intra- and subretinal fluid
no resolution
p=0.050*
p=0.695
p=0.009*
p=0.026*
PED height in micrometers
450
400
350
300
250
200
150
100
50
0
0.064
0.001**
0.514
Ranibizumab
Aflibercept
0
M-9
M0
M3
M9
Time point

Lien vers l'article en ligne:

http://journals.lww.com/retinajournal/Abstract/2016/05000/PIGMENT_EPITHELIAL_DETACHMENT_RESPONSE_TO.5.aspx