Monthly treatment of ranibizumab in vascular pigment epithelium detachment due to age-related macular degeneration: a prospective multi-center study

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Summary Statement: Monthly ranibizumab injections in vascularized pigment epithelial detachment (vPED) secondary to AMD represent an effective regimen regarding visual acuity and morphologic characteristics. vPED patients should be screened for morphologic risk factors for RPE tear development. An adapted treatment regimen in such patients may lower the incidence of RPE tears.

ABSTRACT

Purpose:

To assess the effects of monthly intravitreal ranibizumab injections in patients with vascularized pigment epithelial detachment (vPED) secondary to age-related macular degeneration (AMD).

Methods:

A total of 40 patients were prospectively analyzed and treated monthly with 0.5 mg ranibizumab injections (ClinicalTrials.gov Ident. NCT00976222). Best-corrected visual acuity (BCVA) and spectral-domain optical coherence tomography (SD-OCT) were evaluated at all visits. Fluorescein angiography and indocyanin green angiography were performed at baseline and quarterly. Change in BCVA, PED greatest linear diameter (GLD) and PED height from baseline to month 12 and the incidence of retinal pigment epithelial (RPE) tears were evaluated. Patients were also analyzed for the following prognostic markers of an impending RPE tear: PED lesion's height and diameter, ratio of choroidal neovascularization (CNV) size to PED size, hyperreflective lines in near-infrared images, microrips and subretinal cleft. Lesions were differentiated between serous vascular PED (group A, 29 patients) and fibrovascular PED (group B, 11 patients).

Results:

Mean BCVA was 58.4 ± 11.7 (A: 58.0; B: 59.1) at baseline and 54.1 ± 15.5 (A: 52.3; B: 58.9) at 12-month follow-up. The mean decrease in PED height was -242.1 ± 285.5 µm (A: -352.4 ± 299.7 µm; B: -51.6 ± 99.5 µm). The mean decrease in PED GLD was -471.8 ± 727.6 µm (A: -738.9 ± 788.2 µm; B: -10.4 ± 185.6 µm). After 3.6 treatments, ten (25 %) patients from group A developed a RPE tear. No tear was documented in group B. Lesion's height and presence of hyperreflective lines differed significantly between patients with and without RPE tear development.

Conclusions:

Ranibizumab is an effective treatment for vPED due to AMD regarding BCVA and morphologic characteristics of vPED lesions. Considering the relatively high rate of RPE

tears serous vascular PED patients should be screened for the presence of morphologic risk factors for RPE tear development. An adapted treatment regimen in such patients presumably makes ranibizumab therapy safer. Future studies must further evaluate the sensitivity and specificity of RPE tear predicting signs in vPED lesion.

INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has become an established treatment for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). In about ten percent of all patients neovascular AMD is associated with a vascularized pigment epithelium detachment (vPED).[1-2]

Large scale multicenter studies such as CATT, IVAN and VIEW showed that monthly anti-VEGF injections in neovascular AMD patients resulted in better functional results compared to a pro-re-nata regimen.[3-5] However, those trials do not finally answer the question if AMD patients with vPED lesions functionally benefit from monthly anti-VEGF injections.

A study by Sarraf and co-workers showed that the incidence of retinal pigment epithelium (RPE) tears increases in vPED patients treated with 2.0 mg ranibizumab compared to 0.5 mg.[6] A higher quantity of anti-VEGF seems to critically increase the contraction of CNV membranes under the surface of the vPED and eventually determines the RPE tear rate in patients at risk. So far, the rate of RPE tear development in vPED patients has not been prospectively analyzed under a fixed monthly regimen and it remains unclear if potentially functional benefits of monthly injections outweigh the risk of RPE tear development or vice versa.

Several prognostic markers for an impending RPE tear have been described such as vPED lesion's height and diameter, hyperreflective lines in near-infrared images, a small ratio of CNV size to PED size, subretinal clefts, microrips and duration of vPED.[6-16]

The aim of our study was to prospectively assess the effects of fixed monthly intravitreal ranibizumab injections in patients with vPED secondary to AMD and to analyze the incidence of RPE tear development with regards to RPE tear risk factors.

METHODS

This study was conducted as a prospective, single-arm, interventional, multi-center study at the Departments of Ophthalmology at the Universities of Muenster, Bonn and Munich, Germany between 2009 and 2013 (ClinicalTrials.gov Ident. NCT00976222). Institutional review board approval was obtained prior to study procedures. Informed consent was obtained from each included study patient. All procedures adhered to the tenets of the Declaration of Helsinki.

Patients were treated monthly with intravitreal 0.5 mg ranibizumab injections. Primary outcome of the study was the change of best-corrected visual acuity (BCVA) under the treatment regimen during a 12-month period. Secondary outcomes were the change in vPED height, vPED diameter, presence of subretinal fluid and the number of RPE tears.

Inclusion criteria were a treatment-naïve vPED lesion associated with CNV due to neovascular AMD and a BCVA of 24 - 73 letters according to the Early Treatment Diabetic Retinopathy Study (ETDRS) score. Exclusion criteria included prior anti-VEGF therapy, subretinal hemorrhage, geographic atrophy, fibrovascular scar, pre-existing tear of the RPE, polypoidal choroidal vasculopathy or any other retinal disease.

At baseline, patients underwent clinical examination including BCVA using ETDRS charts, SD-OCT, fluorescein angiography (FA) and indocyanin green angiography (ICGA) (Spectralis HRA; Heidelberg Engineering, Germany). During follow-up, BCVA and SD-OCT were evaluated at all visits. FA and ICGA were performed at baseline and quarterly. All patients received monthly ranibizumab injections.

Patients were retrospectively analyzed for the following prognostic markers of an impending RPE tear: (1) PED lesion’s height, (2) PED lesion’s diameter, (3) ratio of CNV size to PED size, (4) hyperreflective lines in near-infrared images, (5) microrips, (6) subretinal cleft.

vPED lesion types

Based on SD-OCT, FA and ICGA, vPED lesions were identified and classified into two forms:

Group A: Serous vascularized PED (svPED) identified by the presence of shading background fluorescence in the area of the PED in the early phase, followed by gradual appearance of a circular zone of intensifying and irregular hyperfluorescent leakage at the margin of the PED corresponding to the CNV. SD-OCT scans show hyperreflective structures underneath the RPE that represent the CNV and fill out only part of the PED cavity.[11]

Group B: Fibrovascular PED (fPED) with underlying occult CNV identified by areas of stippled hyperfluorescence and signs of leakage in the later phases.[17] In SD-OCT scans, the PED lesion's cavity appears to be completely filled out with the CNV membrane.[11]

Statistical methods

Data were analyzed for the entire patient group, for the svPED group, for the fPED group and the group of patients that developed an RPE tear. BCVA data were calculated by Wilcoxon matched-pairs signed rank test. Morphological data were calculated by Mann-Whitney test. Statistical significance was set at $p < 0.05$.

RESULTS

40 patients completed the study protocol. Mean age was 73.4 ± 5.38 and 23 patients were female. The mean number of injections per patient was 11.3. 29 patients revealed criteria of a svPED and 11 patients showed typical characteristics of a fPED. Mean BCVA was 58.4 ± 11.7 (A: 58.0; B: 59.1) at baseline and 54.1 ± 15.5 (A: 52.3; B: 58.9) at 12-month follow-up (p = 0.135; A p = 0.097; B p = 0.813) (Figure 1). Mean BCVA in the patient group that developed a RPE tear during the follow-up period was 65.5 at baseline and 49.3 at 12-month follow-up (p = 0.074).

The PED height significantly decreased from 565.4 ± 305.1 µm at baseline to 401.5 µm ± 252.0 at three months, 348.3 µm ± 190.9 at six months, and 323.3 µm ± 187.1 at 12 months treatment. The mean decrease after 12 months was – 242.1 µm ± 285.5 (p = < 0.01). The values for group A decreased from 658.9 µm ± 330.5 at baseline to 469.2 µm ± 283.1 at 3 months, to 380.7 µm ± 237.0 at 6 months and to 306.5 µm ± 215.6 at 12 months after treatment resulting in a significant difference compared with the baseline value (- 352.4 ± 299.7 µm; p = < 0.01). The baseline values for group B were 403.9 ± 154.9 µm, and the values at 3, 6 and 12 months after treatment were 353.2 ± 111.3 µm, 359.7 ± 109.3 µm, and 352.3 ± 117.7 µm, respectively, which showed no significant change to baseline values (-51.6 ± 99.5 µm) (Figure 2).

The mean decrease in PED GLD was -471.8 ± 727.6 µm (group A: -738.9 ± 788.2 µm; group B: -10.4 ± 185.6 µm, all not significant) (Figure 2).

Lesion's height was 876.2 ± 315.6 µm in the RPE tear group and 565.4 ± 305.1 µm in the group without RPE tear (p=0.0125). Hyperreflective lines were present in 32.5 % of all patients. (RPE tear group: 70%; no RPE tear group: 19.4%; p = 0.006). PED lesion's diameter was 2767.7 µm ± 1276.4 (no RPE tear = 2616.7 µm ± 1060.5; p = 0.20). The ratio of CNV size to PED size was 0.24 (no RPE tear = 0.56; p = 0.0133). A microrip was observed in one patient. A subretinal cleft was observed in eleven patients (Group A: 3 patients; group B: 8 patients) (no RPE tear group: 9 patients; p = 0.696). Figure 3 shows data of prognostic markers of an impending RPE tear.

All patients showed subretinal fluid at baseline particularly accumulating at the margin of vPED lesions. After the first injection, subretinal fluid was completely resolved in 32.5 % of patients (Group A: 34.5 %; group B: 27.3 %) 62.5% after two injections [A: 68.9 %; B: 45.5 %], 72.5 % after three injections [A: 93.1%; B: 45.5%]. In the RPE tear group, 60% of patients showed no subretinal fluid after two injections. After 3.6 treatments, ten (25 %) patients of group A developed a RPE tear. No tear was documented in group B.

DISCUSSION

In the CATT, IVAN and VIEW studies, patients in the monthly treatment arms revealed better visual acuity results compared to treatment as needed.[3-5] For instance, patients in the CATT trial gained 8.8 letters after two years in the monthly treatment group compared to 6.7 letters in the group that was treated as needed. Whether a monthly treatment regimen in vPED patients proves to be beneficial appears questionable with regards to the presumed pathophysiology of RPE tear development under anti-VEGF therapy. Basically, the development of RPE tears may occur as a spontaneous event.[18] For many years numerous authors have postulated a RPE tear mechanism based on contraction of fibrovascular membranes.[19-22] However, since the beginning of the anti-VEGF era, an increase in the RPE tear incidence in AMD patients has been observed, which was interpreted as a confirmation of the established theory of tractional forces causing the tear event. Anti-VEGF agents cause an increase in contraction of CNV membranes adherent to the undersurface of the RPE inducing shrinkage of the RPE, which causes an increased tension on the surface of the vPED cavity and eventually results in the anatomic failure of the RPE at the junction of attached and detached RPE. Based on these observations one may hypothesize that the higher the quantity of anti-VEGF injected intravitreally the higher the contraction of the CNV membrane and the stronger the traction forces acting on the RPE.

Data from our study reveal a fairly high number of RPE tears in comparison to previous prospective vPED studies that used a pro re nata treatment scheme. An obvious explanation may be that monthly injections result in a certain anti-VEGF quantity that exceeds a critical threshold in such high risk patients. Above this threshold the risk of RPE tear development continuously rises with increasing amounts of anti-VEGF. A study by Sarraf and co-workers supports this notion. They prospectively treated patients with vPED with different dosages of ranibizumab and interestingly they found that 80% of RPE tears occurred in the high-dose 2.0-mg group suggesting that this high dosage regimen also leads to intravitreal anti-VEGF quantities above a critical threshold.[6]

Notably, RPE tears in our study occurred exclusively in the group of svPED lesions and no RPE tear developed in the fPED group. The mechanical proportions in these two vPED types presumably explain this clear-cut difference. In fPED, the lesion cavity is entirely filled by the CNV membrane, therefore, contraction forces in response to anti-VEGF therapy may spread evenly over the entire PED lesion exposing the RPE monolayer to bearable mechanical stress. Whereas, in svPED the mechanical situation is comparably unfavourable as the lesion is for the most part filled by a fluid bleb and only partly filled out by the CNV. Contracture of the CNV adherent to the undersurface of the RPE applies the maximum traction at the junction of the attached and detached RPE lying perpendicular to the CNV.[23]

Notably, there is a striking difference between the svPED lesions and the fPED lesions in terms of PED lesion height and PED GLD. The svPED architecture reacts with distinctly more morphologic dynamics to the anti-VEGF therapy compared to the fPED type which appears to remain inert in its lesion configuration. These morphologic dynamics involve a higher amount of mechanical stress, which presumably explains the higher incidence of RPE tears in the svPED group.

The large multicenter studies in neovascular AMD showed that the biggest change in retinal thickness occurs after the first treatment, which suggests that the first anti-VEGF injection has the largest morphological impact on the retina and stresses the RPE the most.[3-5] In accordance with previous studies, most RPE tears in our study occur during the first three injections.[8,24] However, in a minor part of three patients RPE tears developed after the first three injections when, interestingly, subretinal fluid had already been resorbed. If treatment in those patients had been paused after the complete resorption of subretinal fluid and a pro-re-nata regimen had begun, those RPE tears may have been prevented.

If subretinal fluid is completely resorbed the lesion should be regarded as inactive and anti-VEGF treatment should be paused.[25] The aim of the intravitreal treatment is not to achieve a maximum flattening of the vPED lesion rather than to assure a total absence of subretinal fluid. Aiming at an excessive flattening of the vPED lesion in the absence of subretinal fluid unnecessarily increases the risk of an RPE tear without any functional benefits.

The fact that subretinal fluid is often already resorbed after the first injection and that most RPE tears occur during the first three injections may suggest that one should prefer a pro-re-nata regimen without an uploading phase of three fixed injections in high-risk serous vascular PED patients. Particularly a complete resorption of subretinal fluid after the very first injection should be interpreted as a strong response to anti-VEGF going along with a high degree of mechanical stress on the RPE.

The analysis of RPE tear risk factors shows that three parameters are important to look at: PED height, PED diameter and CNV/PED ratio. PED height in RPE tear patients in our study was 721.6 µm, which is in accordance with Doguizi et al who calculated a PED height of 580 µm above which this parameter represents a significant risk factor for tear development.[8] Similarly, Sarraf et al described a height of 550 µm as a high-risk factor for the subsequent development of an RPE tear, and additionally Leitritz and co-workers described an increasing probability of RPE tears particularly beyond the height of 400 µm.[6,14]

Chan and colleagues reported that a lesion diameter of > 1397 µm represents a significant risk factor for RPE tear development.[7] Comparably, our patients showed a lesion diameter of 2767.7 µm.

Chan et al firstly described the concept of a CNV/PED ratio representing another crucial risk factor for tear development.[12] Our data supports this notion as our RPE tear patients showed a significantly smaller CNV/PED ratio compared to non RPE tear patients as well.

In accordance with previous reports, our analysis revealed clear data that confirm hyperreflective lines in infrared images as a predictive factor.[11] Hyperreflective lines are not present in all RPE tear patients. Possibly, hyperreflective lines in the infrared modality exist only for a short period of time prior to the RPE tear event and therefore this phenomenon may well occur in between study visits and may not always be detected. Secondly, a certain amount of traction must be present to form the folds in the RPE that correspond to the hyperreflective lines in infrared images. Certain patients may have a poorly resistant RPE monolayer so that already a small amount of traction is sufficient to cause a tear and yet, insufficient to make the hyperreflective lines appear. The parameters subretinal cleft and

microrip do not show a significant correlation to RPE tear development. The relevance of these criteria remains unclear as they have only been described in case series so far. Their incidence seems to be low. Nevertheless, their sensitivity to predict an RPE tear development should be further addressed in future studies.

The study is limited by several factors. Despite the high rate of RPE tears the absolute number remains obviously small. However, a prospective study on RPE tear development in vPED remains a challenge as it requires a large number of included patients as well as a huge amount of study center infrastructure. Nevertheless, a future prospective study with a higher number of patients developing an RPE tear is necessary to firstly verify each potential risk factor and secondly to stratify the weight of each risk factor. This way it would be possible to quantify the risk of an RPE tear development of each individual vPED patient undergoing anti-VEGF therapy. In this study, the analysis of predictive factors was performed retrospectively.

In conclusion, ranibizumab is an effective treatment for vPED due to AMD regarding BCVA and morphologic characteristics of vPED lesions. Considering the relatively high rate of RPE tears a fixed monthly anti-VEGF treatment appears to exceed a critical threshold in serous vascular PED high risk patients. An adapted as needed treatment regimen in such patients presumably makes intravitreal ranibizumab therapy safer. Besides, patients should be screened for the presence of morphologic risk factors for RPE tear development before and during treatment. Future studies must further evaluate the sensitivity and specificity of such RPE tear predicting signs in vPED lesion.

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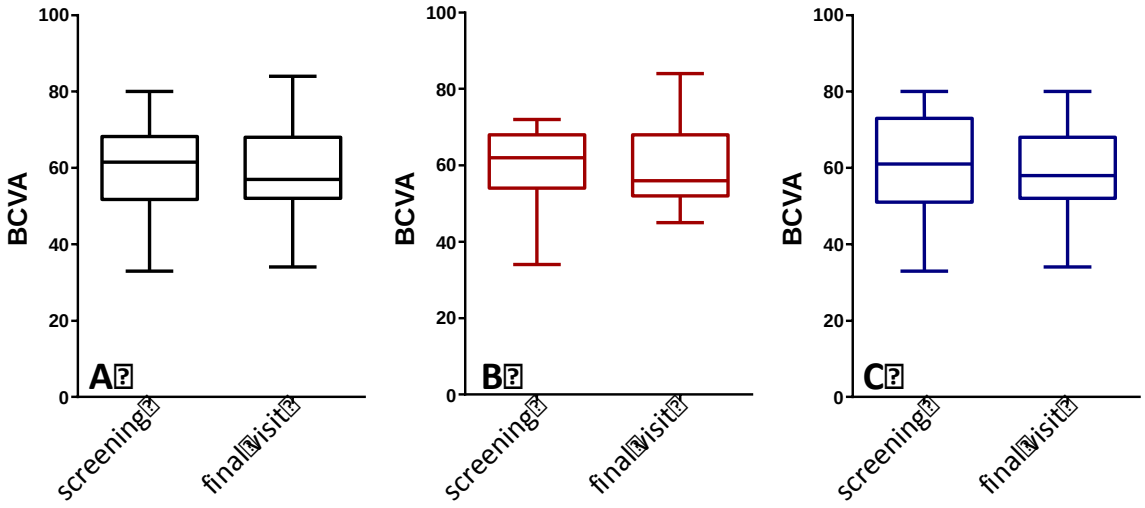
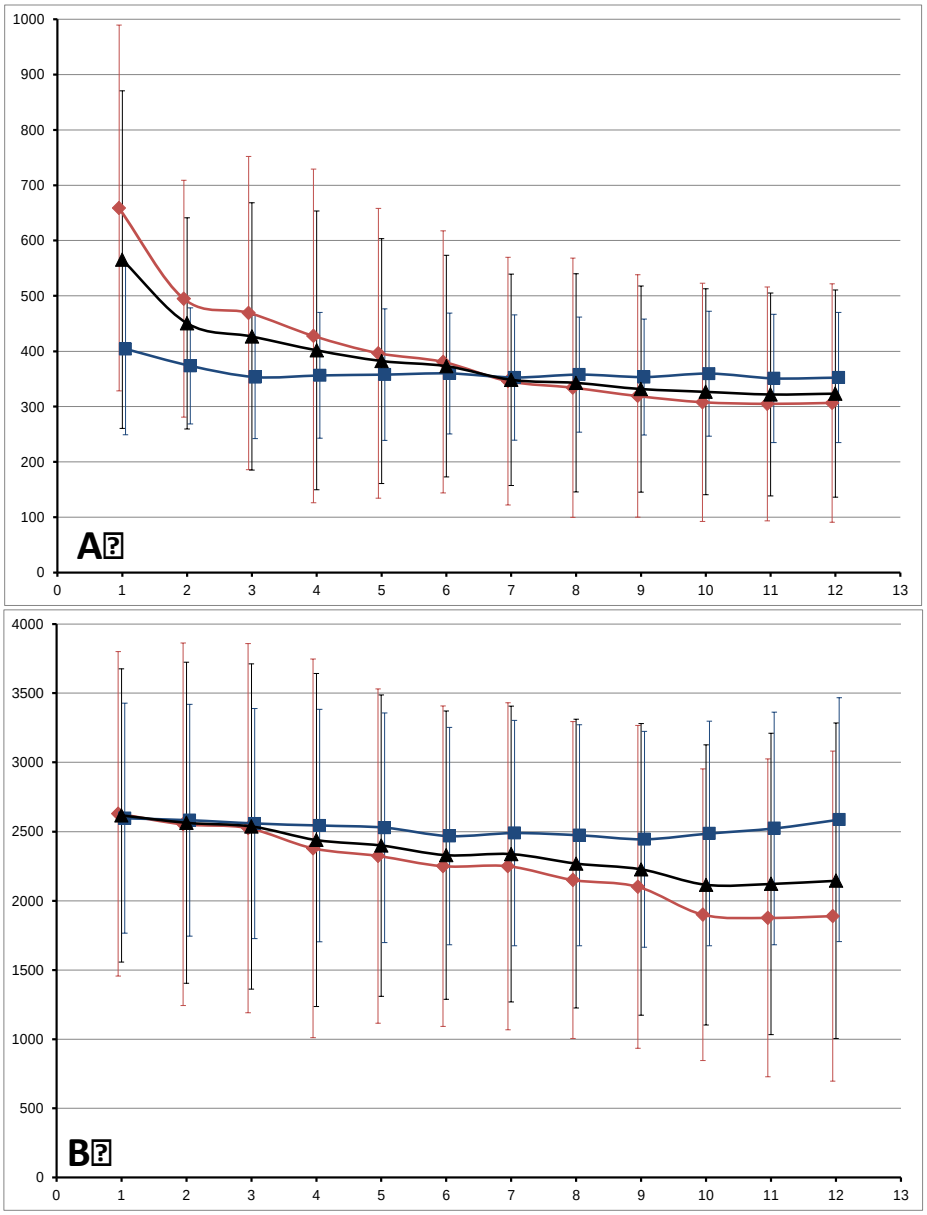
FIGURE AND LEGEND

Figure 1

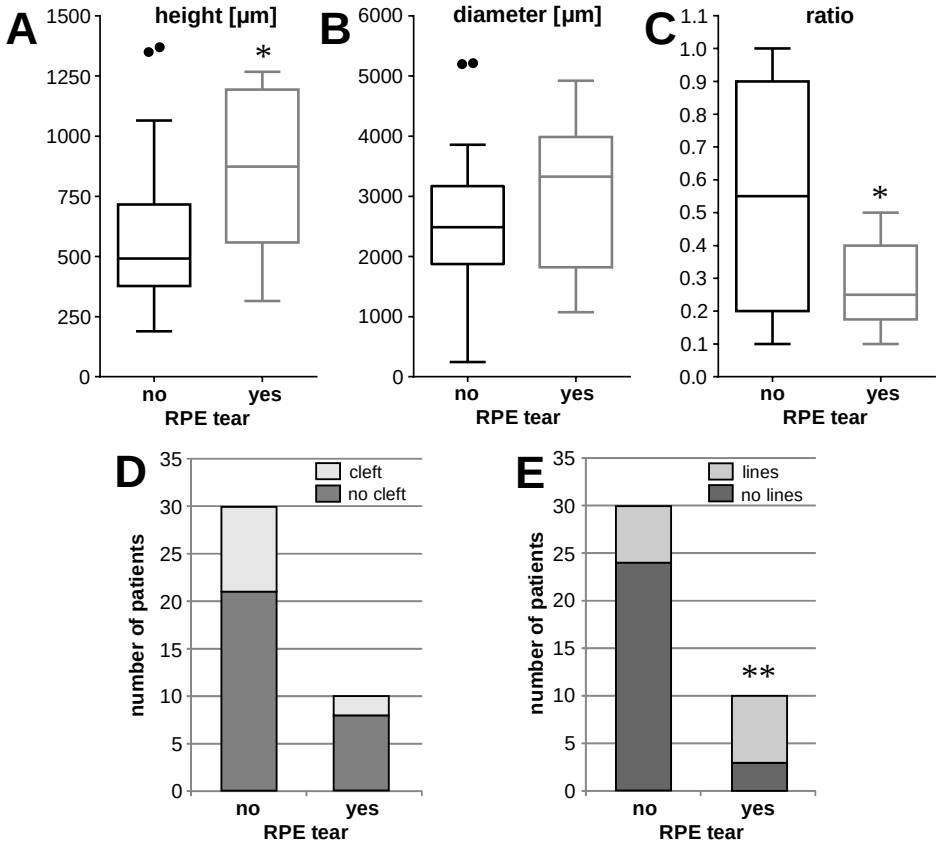


[A-C] Box-plot diagrams showing best-corrected visual acuity at screening and 12-month final visit of **[A]** all patients **[B]** serous vascularized pigment epithelium detachment (PED) group and **[C]** fibrovascular PED group.

Figure 2



[A-B] Box-plot diagrams showing **[A]** maximum pigment epithelium detachment (PED) height [µm] and **[B]** maximum PED diameter [µm] during 12-month study period. Black line: all patients, red line: serous vascularized PED group, blue line: fibrovascular PED group.



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316 **Figure 3**

317 **[A-C]** Box-plot diagrams showing analysis of predictive signs for retinal pigment epithelium
318 (RPE) tear development in patients that developed an RPE tear during follow-up and patients
319 that did not. **[A]** Pigment epithelium detachment (PED) lesion's height, **[B]** PED lesion's
320 diameter and **[C]** ratio of choroidal neovascularization size to PED size, **[D-E]** Bar charts
321 illustrating the prevalence of **[D]** presence of a subretinal cleft and **[E]** presence of
322 hyperreflective lines in near-infrared images.