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CLINICAL INVESTIGATION

Correlation between macular structure and function in patients with age-related macular degeneration treated with intravitreal ranibizumab: 12-month-results

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Abstract

Purpose To determine the significance of the correlation between optical coherence tomographic (OCT) findings and focal macular electroretinograms (fmERG) at 12 months after beginning intravitreal injections of ranibizumab (IVR) in eyes with age-related macular degeneration (AMD).

Study design Prospective, clinical study.

Method We studied 28 eyes of 28 patients with AMD treated with IVR at monthly intervals for the initial three months. Additional IVR was given according to a *pro re nata* (PRN) regimen. OCT and fmERGs were performed preoperatively and at 3 and 12 months postoperatively. The fmERGs were elicited by a 15° white stimulus spot centered on the fovea. The thickness of the inner, middle, and outer layers of the retina and also of the serous retinal detachment (SRD) and pigment epithelial detachment (PED) in the horizontal and vertical meridians at 1.2 mm from the fovea (parafoveal) were measured in the OCT images.

Results The b-wave amplitude at 12 months was significantly correlated with the thicknesses of the outer retinal layer, SRD, and PED (P=0.001–0.02). Multiple regression analyses showed that the outer retinal layer thickness was an independent determinant (P= 0.0001). The changes in the b-wave amplitude between the baseline and 12 months were significantly correlated with the changes in the SRD thickness (P=0.006). The changes in the b-wave amplitude during the PRN period were significantly correlated with the changes in the PED thickness (P=0.02).

Conclusions At 12 months after beginning treatment, the reduction in the SRD thickness affects macular function recovery. As recurrences of the PED can occur during the PRN period, control of the PED is necessary to obtain good macular function for the long term.

Keywords Age-related macular degeneration · Intravitreal ranibizumab · Focal macular electroretinogram · Serous retinal detachment · Pigment epithelial detachment

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness and severe visual impairment in the elderly. The number of AMD patients in Japan has increased due to an increase in the elderly population and westernization of lifestyle. In a recent survey, AMD was found to be the fourth leading cause of vision-threating disorders in Japan. In the 1998 Hisayama study, the prevalence of late AMD was 0.67% of the population over the age of 50 years, but in a 2007 survey it increased to 1.4% [1, 2].

The main pathology of the exudative or wet type of AMD is the development of choroidal neovascularization (CNV) accompanied by exudative changes and bleeding.

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These changes eventually lead to irreversible reduction in vision. Vascular endothelial growth factor (VEGF) plays an important role in the development of CNVs, and thus, anti-VEGF therapy has become the common treatment for CNVs associated with exudative AMD. Large, multicenter, randomized, double-masked, and controlled clinical trials show that intravitreal injections (IVR) of ranimizumab, a recombinant, humanized monoclonal anti-VEGF-A antibody which binds to the antigen-binding fragment (Fab), can lead to significant improvement in the central vision in patients with exudative AMD [3–5]. It is reported that the incidence of blindness and sight impairment in AMD patients receiving ranibizumab is decreasing yearly [6]. Intravitreal injections of bevacizumab and aflibercept lead to similar results [7–9].

The visual function has been assessed mainly by the best-corrected visual acuity (BCVA) in clinical trials to determine the efficacy of the anti-VEGF drugs in AMD patients [4–10]. Although the BCVA is determined by foveal function, it does not necessarily reflect the overall improvement in visual function. Because IVR decreases the exudation associated with CNV in the macular area, it improves the function of not only the fovea but also the parafoveal area. Using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) Yuzawa et al. conclude that there was an improvement of the vision-related quality of life (VRQoL) after anti-VEGF treatment. At week 52, the NEI VFQ 25 total score and sub scores were significantly improved after treatment of the affected eyes with either ranibizumab or aflibercept [11].

The macular function of AMD patients treated with anti-VEGF therapy has also been assessed by electroretinography (ERG) including the focal macular ERGs (fmERGs) [12–16]. The fmERGs recorded by the Miyake technique [17, 18] has an advantage over the mfERGs when examining eyes with poor central vision, as well as in patients with AMD, by being able to record the fmERGs while viewing the location of stimulus spot on the macula. Determining the correlation between the macular structure and function in patients with AMD should allow clinicians to determine the macular function from the macular structures. In addition, the recovery of the structural integrity of the macula could possibly enable clinicians to estimate the recovery of the macular function in AMD patients following treatment. Thus, understanding the relationship between the macular thickness and macular function should provide useful information on the benefits of anti-VEGF treatments for the macular function.

We have reported that the macular function before treatment assessed by fmERGs was correlated with the thicknesses of the parafoveal outer retinal layer and serous retinal detachments (SRDs) in patients with AMD. In addition, the reduction in the thickness of the SRD after 3 consecutive IVR injections affected the recovery of the macular function significantly [19]. However, AMD requires long-term management in the maintenance phase, and in most patients the treatment could continue indefinitely. Thus, the long-term consequences of anti-VEGF therapy are just as important.

The purpose of this study was to determine the structural parameters of the retina that are significantly correlated with the macular function evaluated by fmERGs in patients with exudative AMD treated with IVRs at 12 months after beginning of treatments.

Methods

Patients

We studied 28 eyes of 28 patients with a CNV secondary to AMD; 18 with typical exudative AMD and 10 with polypoidal choroidal vasculopathy (PCV). In all, 20 men and 8 women whose mean age was 72 ± 8 years (± standard deviation) with a range of 50 to 84 years were enrolled. All patients had a comprehensive ophthalmological examination including measurements of BCVA with a Snellen chart, slit-lamp biomicroscopy, and indirect ophthalmoscopy both before and throughout the follow-up period. Fluorescein angiography and indocyanine green angiography were performed before the treatment. Patients with history of other retinal diseases treated with pharmacologic agents including verteporfin photodynamic therapy, anti-VEGF agents, or steroid therapy, and those with a history of vitrectomy or glaucoma surgery were excluded. We included patients with unilateral exudative AMD with normal contralateral eyes determined by OCT and angiography.

This research was conducted in accordance with the institutional guidelines of Iwate Medical University, and the procedures conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients after a full explanation of the nature of the investigations.

Intravitreal injections of ranibizumab

A 30G needle was inserted through the pars plana to inject 0.5 mg/0.05 ml of ranibizumab into the vitreous. The injections were made at monthly intervals for three months. Later, additional IVR was given according to the optical coherence tomography (OCT)-guided variable-dosing regimen used in the PrONTO study [20]. At each visit, the BCVA was examined, and OCT and ophthalmoscopy were used to assess the ocular fundus.

Spectral-domain optical coherence tomography (SD-OCT)

The retinal morphology was evaluated by spectral-domain OCT (SD-OCT, Spectralis, Heidelberg Engineering). The SD-OCT scans passed through the fovea horizontally and vertically. Parafoveal measurements were made in the horizontal and vertical meridians at 1.2 mm from the fovea according to a previous report (Fig. 1a) [21]. The parafoveal thicknesses of the retinal layers were measured and averaged for statistical analyses. The retinal thickness was divided into an inner layer which extended from the internal limiting membrane (ILM) to the inner plexiform layer (IPL; Fig. 1c, 2), a middle layer which was measured from the inner nuclear layer (INL) to the outer plexiform layer (OPL;, Fig. 1c, 3), and an outer layer which was measured from the outer nuclear layer (ONL) to the ellipsoid zone (Fig. 1c, 4). The thickness of the SRD was measured from the ellipsoid zone to the highly reflective retinal pigment epithelium (RPE; Fig. 1c, 5), and the pigment epithelial detachment (PED) was measured from the RPE to Bruch's membrane (Fig. 1c, 6). The full layer parafoveal thickness was measured from the ILM to Bruch's membrane (Fig. 1c, 1 = 2 + 3 + 4 + 5 + 6).

Focal macular ERG (fmERG) recordings

The pupils were dilated to approximately 8 mm in diameter by topical 0.5% tropicamide and 0.5% phenylephrine HCL. The fmERGs were recorded from the macular area by the methods developed by Miyake et al. [17, 18]. The stimulus system was integrated into an infrared fundus camera (Mayo Co). The stimulus spot was 15° in diameter centered on the fovea, and the position was confirmed by viewing the ocular fundus in the monitor of the fundus camera. The intensity of the white stimulus was 165 cd/m^2 and background light was 6.9 cd/m^2. The stimulus duration was 10 msec. The stimulated area overlapped the area from which the OCT image were recorded (Fig. 1A). The fmERGs were picked-up by a Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic Laboratories). A chlorided silver electrode was placed on the left ear lobe as the ground electrode.

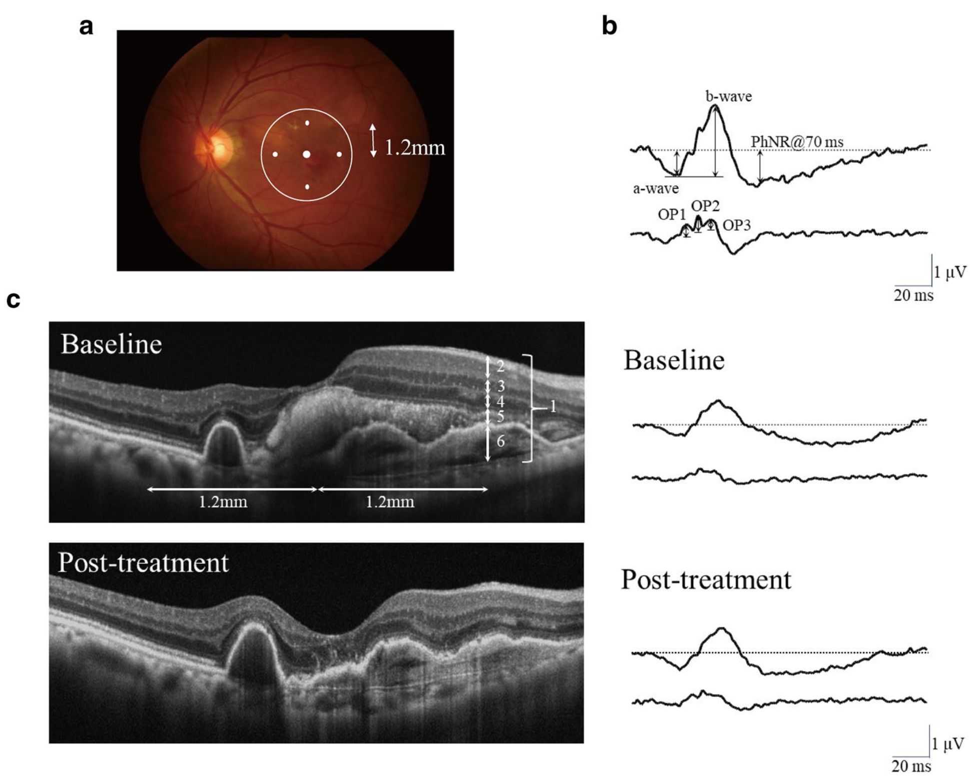

Fig. 1 SD-OCT images and fmERGs recorded from a patient with exudative AMD before and 12 months after beginning the IVR injections. **a** The retinal loci where the retinal structures were measured in the SD-OCT images are indicated by white dots. The retinal area where the fmERGs were recorded from is shown by the white circle. **b** The method used for measuring amplitudes of the a- and b-waves, PhNR, and sum of the oscillatory potentials (ΣOPs; OP1+OP2+OP3) of the fmERGs d. **c** SD-OCT images and fmERGs recorded from a representative case of exudative AMD at the baseline and after IVR injections. In the SD-OCT images the parafoveal retina was measured full layer (1) and segmented into an inner (2), middle (3), and outer layer (4). The serous retinal detachment (SRD; 5) and pigment epithelial detachment (PED; 6) are also shown. *PhNR* photopic negative response, *OP* oscillatory potential, *SD-OCT* spectral-domain optical coherence tomographic, *fmERGs* focal macular electroretinograms, *AMD* age-related macular degeneration, *IVR* intravitreal ranimizumab

The responses were digitally band pass filtered from 5 to 200 Hz for the a- and b-waves and the photopic negative responses (PhNRs), and from 50 to 500 Hz for the oscillatory potentials (OPs; Neuropack, MEB 9102, Nihon Koden). Approximately 300 responses were summated at a stimulation rate of 5 Hz for the fmERGs. The a- and b-wave amplitudes were measured from baseline to the trough of the first negative response and from the first trough to the peak of the following positive wave (Fig. 1b). The PhNR amplitude was measured from the baseline to the negative trough at 70 msec according to the findings in earlier studies [22, 23]. The amplitudes of the OP1, OP2, and OP3 were measured and summed, and designated as the ΣOPs as reported [22, 24].

Statistical analyses

Kruskal-Wallis tests were used to determine the significance of the differences in the pre- and post-treatment values. Dunn's post hoc tests were used for multiple comparisons among the groups. Pearson's coefficient of correlation was calculated to determine the degree of correlation between the structural and functional parameters. Multiple linear regression was used with stepwise selection of variables with significance in the linear regression analysis. The statistical analyses were performed with SPSS software version 20.0 (SPSS, Inc). A $P < 0.05$ was taken to be statistically significant.

Results

Changes in best-corrected visual acuity (BCVA) and foveal thickness

The BCVA was 0.54 ± 0.33 logMAR units at the baseline, and was significantly improved to 0.37 ± 0.34 logMAR units at 3 months after beginning the IVR therapy ($P < 0.001$). At 12 months, the BCVA was 0.45 ± 0.37 logMAR units, worse than at 3 months, but still significantly better than the BCVA at baseline ($P < 0.01$).

The foveal thickness was 372 ± 106 μm at baseline, and was significantly reduced to 259 ± 80 μm at 3 months after the beginning IVR ($P < 0.001$). However, the foveal thickness at 12 months was 340 ± 134 μm which was not significantly different from that at baseline and was significantly worse than at 3 months ($P < 0.01$).

Changes in focal macular ERGs (fmERGs)

The changes in the amplitudes of the different components of the fmERGs after the IVR injections are plotted in Figure 2. Before treatment, the amplitudes of all components were significantly smaller in the affected eyes than in the unaffected fellow eyes (Fig. 1b). At 3 months after beginning the IVR injections, the amplitudes of all components of the fmERGs were significantly increased relative to the corresponding baseline values (Fig. 2a–d). Similarly at 12 months, the a- and b-waves, and ΣOPs amplitudes of the fmERGs were significantly larger than the baseline values ($P < 0.05$ to $P < 0.005$, Fig. 2a, b, d). However, the implicit times of the a- and b-waves were not significantly changed after the treatment. In addition, the amplitude ratio, the b/a-wave, was not significantly changed after the IVRs.

Changes of parafoveal thicknesses

The changes in the parafoveal thicknesses after IVRs are plotted in Figure 3. The thicknesses of the full, inner, and middle layers, and the SRD were significantly reduced at 3 months after beginning the IVRs relative to the baseline (Figs. 3a,–c, e). In addition, significant reductions in the full layer and SRD thicknesses were observed at 12 months compared to the baseline (Fig. 3a, e). The PED thickness was significantly increased at 12 months compared to 3 months after beginning the IVRs (Fig. 3f). The outer layer thickness was not significantly different from the baseline values at any time (Fig. 3d).

Correlations between parafoveal structures and b-wave amplitude of fmERG at 12 months

Linear regression analyses were performed between the parafoveal structural parameters and the b-wave amplitude of the fmERGs at 12 months after beginning the IVR injections (Fig. 4). The full layer thickness was significantly correlated with the b-wave amplitude ($R = -0.41$, $P = 0.03$; Fig. 4a). In addition, the b-wave amplitudes were significantly correlated with the thickness of the outer layer ($R = 0.62$, $P = 0.001$, Fig. 4d), the SRD ($R = -0.49$, $P = 0.02$, Fig. 4e), and the PED ($R = -0.54$, $P = 0.003$, Fig. 4f). On the other hand, the b-wave amplitude was not significantly correlated with the other structural parameters including the inner and middle layer thicknesses (Fig. 4b, c).

Multiple regression analyses with stepwise selection of variables showed that the parafoveal outer layer thickness was an independent determinant of the b-wave amplitude of the fmERGs at 12 months after beginning the IVR injections ($P = 0.0001$).

A correlation diagram between other fmERG components and each retinal layer thickness of the parafovea at 12 months is shown in Table 1. All components including the a- and b-waves, PhNR, and ΣOPs were significantly correlated with the parafoveal outer layer, SRD, and PED thicknesses. Based on these results, we conclude that it is sufficient to choose the

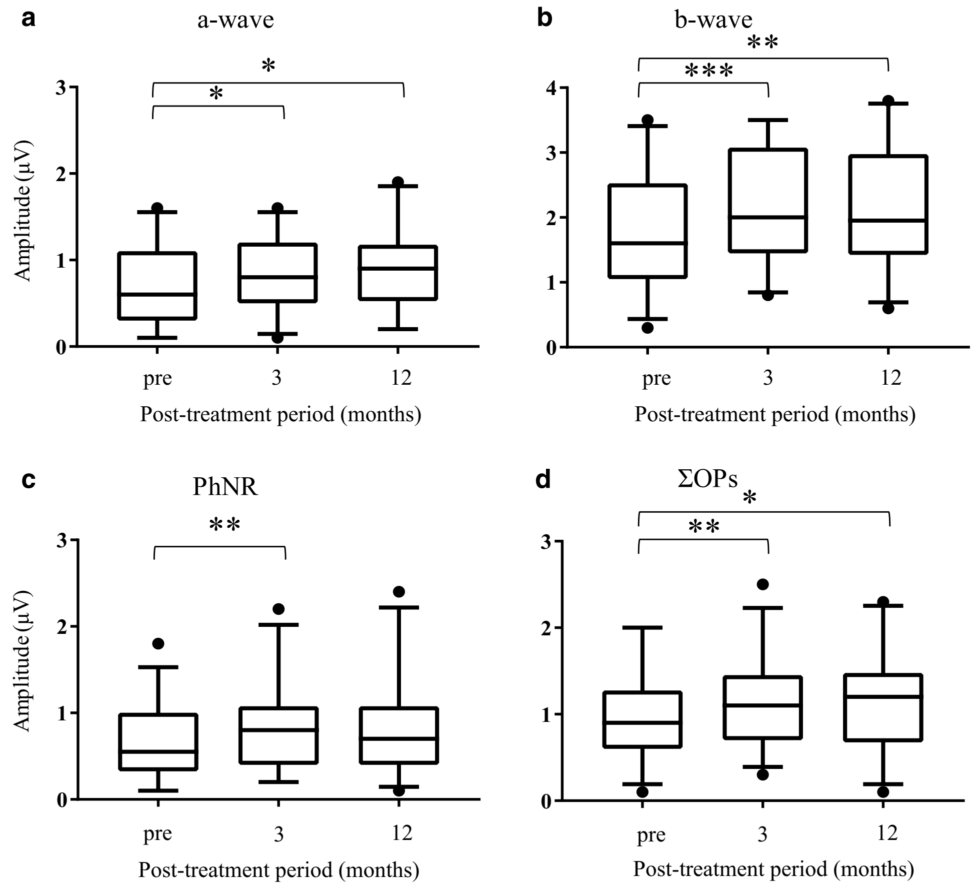

Fig. 2 Amplitudes of the a- (**a**) and b-waves (**b**), PhNR (**c**), and the sum of the oscillatory potentials (ΣOPs, **d**) of the fmERGs. The boxes on the left represent values before (baseline), the middle boxes represent 3 months after the IVR and the right boxes represent 12 months after the IVR injections. The boxes represent 25% to 75% interquartile ranges. The horizontal line represents median values, and the bars represent the 5% and 95% confidence intervals. Dots represent individual data that fell beyond the 5–95% confidence intervals. *PhNR* photopic negative response, *OP* oscillatory potential. *P <0.0005; **P <0.0001

b-wave amplitude as a representative component for evaluating the correlations with each parafoveal retinal thickness.

Correlations between improvement of parafoveal structures and b-wave amplitude of fmERG at 12 months

Linear regression analyses were performed to determine the correlations between the improvement in the parafoveal thickness and the b-wave amplitudes (Fig. 5). The differences in each parafoveal layer thickness between the baseline and 12 months after beginning IVRs are plotted against the differences of the focal b-wave amplitude. The focal b-wave amplitude recovery was significantly correlated with recovery of the parafoveal SRD thickness (R = −0.51, P = 0.006, Fig. 5e). The differences in the full layer, inner layer, middle layer, outer layer, and PED thicknesses were not significantly correlated with the recovery of the b-wave amplitude (Fig. 5a–d, f).

Correlation between changes of parafoveal structures and b-wave amplitude of fmERG during PRN treatment period

The correlation between the parafoveal thickness changes and the b-wave amplitude of the fmERGs changes during the PRN treatment period is shown in Figure 6. Linear regression analysis was performed. The differences in each parafoveal layer thickness between 3 and 12 months after beginning IVRs are plotted against the differences in the focal b-wave amplitude. The focal b-wave amplitude change was significantly correlated with the change in the parafoveal PED thickness (R = −0.44, P = 0.02, Fig 6f). For other structural parameters including the full layer, inner layer, middle layer, outer layer and SRD thicknesses, no significant correlation with the change in the b-wave amplitude was found (Fig. 6a–e).

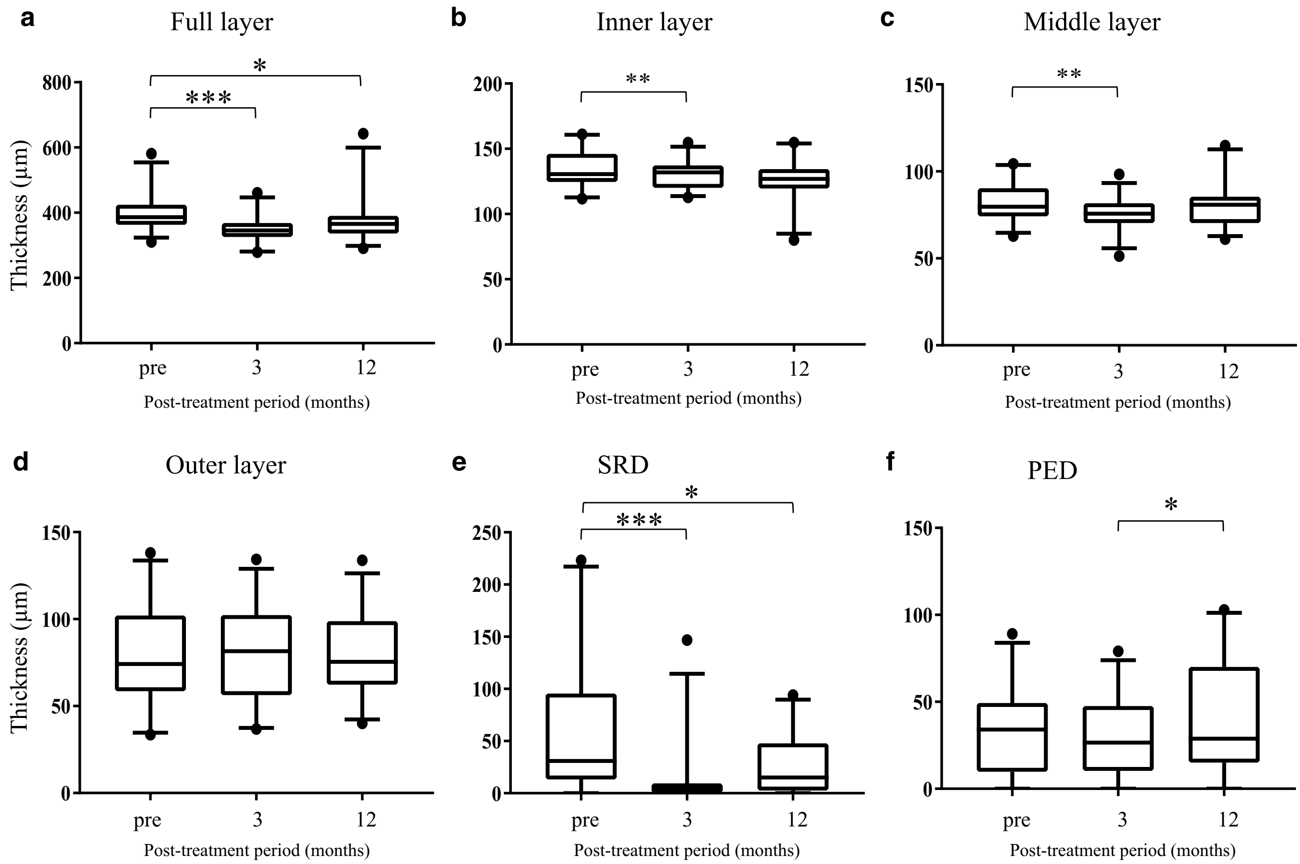

Fig. 3 Full layer thickness (**a**) and individual layer thickness (**b**–**f**) of the parafoveal region are plotted for the values at the baseline (left boxes), The middle boxes at 3 months and the right-hand boxes at 12 months after IVR injections. The boxes represent the 25% to 75% interquartile ranges. The horizontal line represents median values, and the bars represent the 5% and 95% confidence intervals. Dots represent individual data that fell beyond the 5–95% confidence intervals. *SRD* serous retinal detachment, *PED* pigment epithelial detachment. *P <0.0005; **P <0.0001

Discussion

The results show that the b-wave amplitudes of the fmERGs were significantly correlated with the thicknesses of the outer layer, the SRD, and PED in the parafoveal regions even 12 months after beginning the IVR treatments.

Structural parameters affecting macular function

In our earlier study, the a-wave amplitudes of the fmERGs were found to be correlated before the treatment only with the thickness of the parafoveal outer layer (R = 0.56, P = 0.001) and the SRD (R = −0.54, P = 0.002) [19]. In the present study, the b-wave amplitude at 12 months was significantly correlated not only with the outer layer and the SRD but also with the PED. This suggests that the PED might have affected the macular function in the later, rather than in the earlier period of the treatment.

Sharma et al. report that the presence of foveal subretinal fluid (SRF) and subretinal RPE fluid had no significant effect on the mean BCVA at week 52 after beginning the anti-VEGF therapy. However, at week 104, the mean BCVA for eyes with foveal SRF was significantly better than those without a foveal SRF. Similarly, the mean BCVA for eyes with foveal sub-RPE fluid was better than in eyes without foveal sub-RPE fluid [26]. It is believed that SRD and PED have negative effects on the macular function, but as Sharma et al. suggest, due to the complicated relationship between the structural damage, e.g., geographic atrophy, losing them may lead to a decrease in macular function. Simader et al. show that baseline PED had a negative effect on the visual outcome only when combined with intraretinal cysts (IRCs) and SRF [25]. A PED may affect the macular function due to the relationship between the SRF and IRCs rather than by acting alone. It is also believed, that in the late stage of treatment the presence of atrophy and scar can affect the macular function leading to further complications [27, 28].

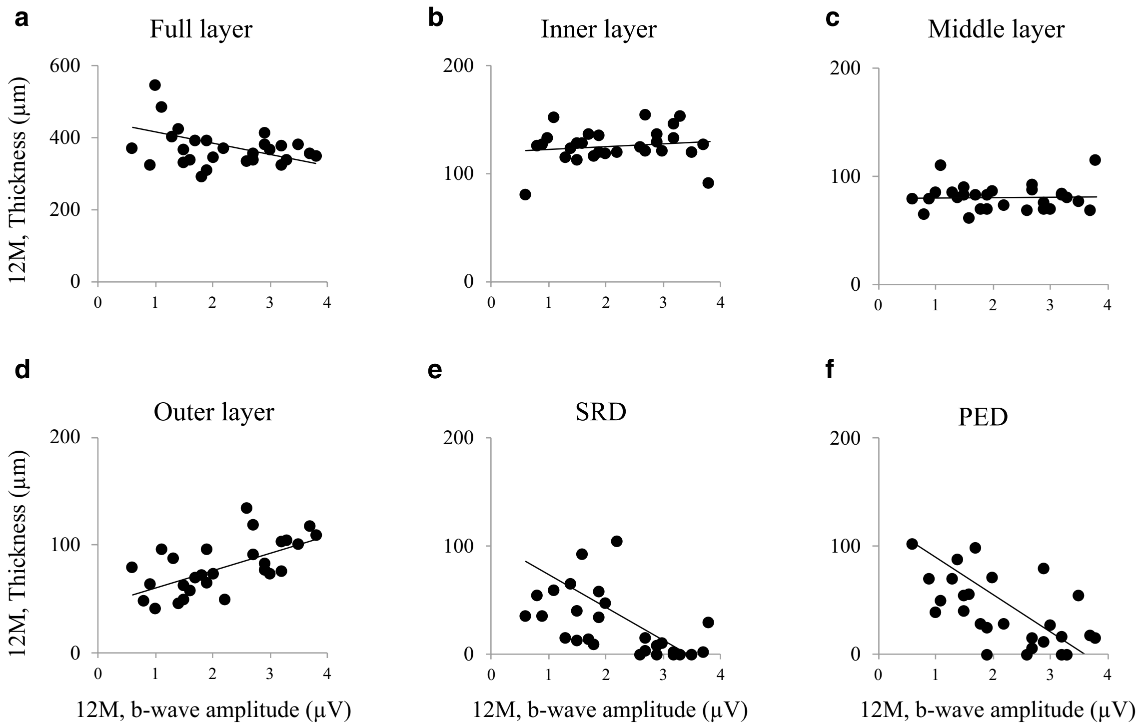

Fig. 4 Correlation between parafoveal structures and b-wave amplitude of fmERG at 12 months. The thicknesses of the full layer (**a**) and each retinal layer including the inner (**b**), middle (**c**), and outer layer (**d**), SRD (**e**) and PED (**f**) are plotted against the b-wave amplitudes. *SRD* serous retinal detachment, *PED* pigment epithelial detachment

Table 1 Correlation coefficients between fmERG components and each retinal layer thicknesses of parafoveal at 12 months

	a-wave	b-wave	PhNR	ΣOPs
Full layer thickness	−0.37 (0.05)	**−0.41 (0.03)**	−0.25 (0.20)	**−0.47 (0.03)**
Inner layer thickness	0.06 (0.75)	0.15 (0.45)	0.18 (0.35)	−0.23 (0.31)
Middle layer thickness	0.11 (0.59)	0.04 (0.82)	−0.08 (0.70)	−0.02 (0.95)
Outer layer thickness	**0.65 (0.0002)**	**0.62 (0.0004)**	**0.63 (0.0003)**	**0.74 (0.0001)**
SRD thickness	**−0.50 (0.009)**	**−0.56 (0.002)**	**−0.53 (0.005)**	**−0.51 (0.02)**
PED thickness	**−0.56 (0.002)**	**−0.62 (0.0004)**	**−0.47 (0.010)**	**−0.61 (0.003)**

fmERG focal macular electroretinogram, *PhNR* photopic negative response, *OPs* oscillatory potentials, parentheses represent *P* values

Effect of *pro re nata* (PRN) treatment on macular structure and function

The increase in the PED thickness during the PRN treatment period significantly deteriorated the macular function. Schmidt-Erfurth et al. show that a switch from a fixed to a flexible PRN regimen led to a progressive reduction in vision only in the group with a primary PED. The PED presented as neovascular activity and was induced by the secondary formation of IRCs [29]. These findings suggest the possibility that PED changes during the PRN treatment period can alter the macular function. It is well known that the visual acuity eventually decreases when the PRN regimen is used during the maintenance phase [30]. In addition, Giansanti reports that the PRN regimen provided insufficient control of the PED [31]. Our results show that there was no further improvement in the fmERGs at 12 months. We assume that multiple recurrences during the maintenance phase treated by the PRN regimen prevented further improvements of the macular function. This raises the possibility that proactive treatment might induce improvements in the macular function during the maintenance phase.

Currently, more and more cases are undergoing maintenance therapy by regular interval injections or 'treat and extend' therapy during the maintenance phase [32]. The differences rising from results of using these regimens and the results of this study are not known, and further investigations are necessary.

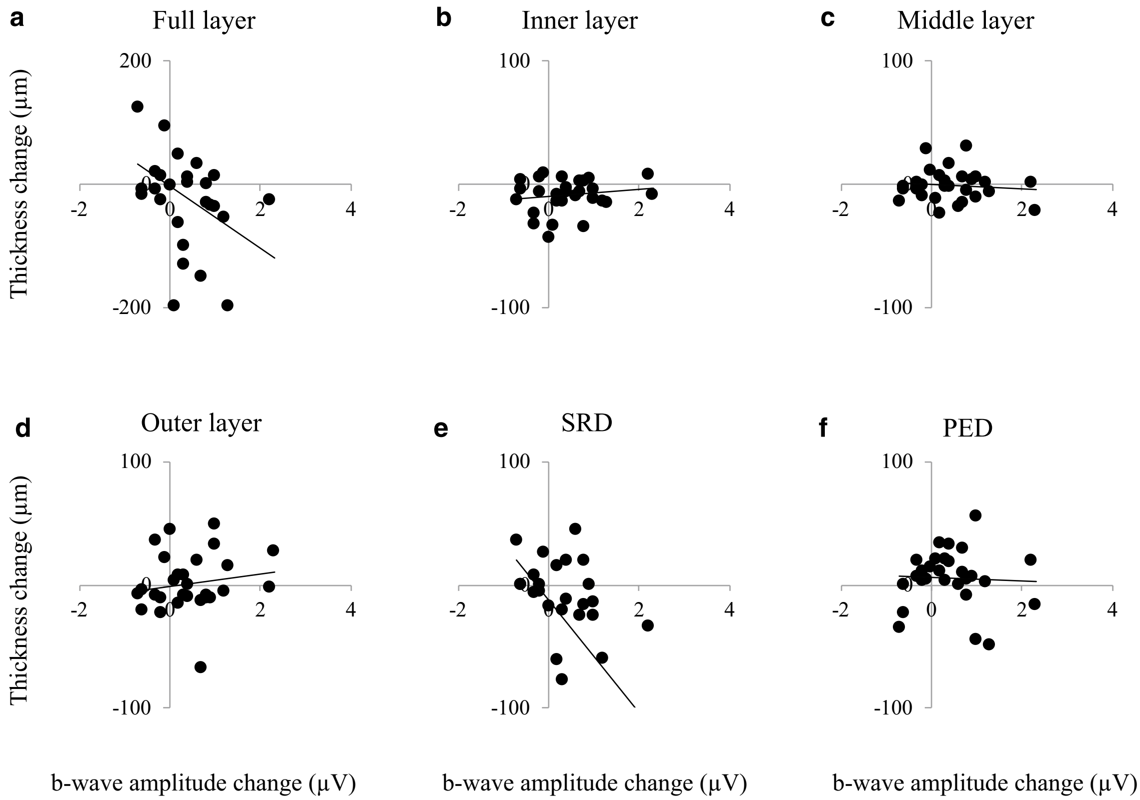

Fig. 5 Correlation between the recovery of the parafoveal structures and b-wave amplitude of the ffmERG at the baseline to 12 months. The recovery of the thicknesses of the full layer (**a**) and each retinal layer including the inner (**b**), middle (**c**) and outer retina (**d**), SRD (**e**) and PED (**f**) are plotted against the b-wave amplitudes

Limitations of study

One limitation of this study was that ranibizumab was the only anti-VEGF agent used. Currently, ranibizumab, bevacizumab, and aflibercept are approved for clinical use to treat eyes with exudative AMD. Clinicians use these drugs according to the disease condition and the patients' wishes. It is reported that aflibercept is more effective than ranibizumab for lesions under the RPE, suggesting that aflibercept may be better than ranibizumab in PED management [33–35]. However, Zinkernagel et al. report that serous PEDs had a fluctuating pattern in spite of bimonthly aflibercept injections in the maintenance phase. Thus, bimonthly aflibercept injections appear not to be sufficient to maintain the morphological improvements after the initial loading dose [36]. Depending on the type of agent used in the treatment, the results may be different from this study. It is believed that the type of PED and the subtype of AMD also influenced the results, thus, a finely divided investigation is necessary.

We defined the differences in structural parameter values during the 9 months from 3 to 12 months as changes in the structures during the PRN treatment period. Repeated monthly IVRs can improve the BCVA over 2 years [9] indicating that structural and functional parameters can continuously change for a long time when treating patients with IVRs according to a PRN regimen. Thus, we cannot say that the differences in the outer retinal and subretinal structures after only 9 months did express only a deterioration during the PRN treatment period. It would be necessary to redefine how to evaluate the changes in the structures during a longer PRN period.

In a previous study [19], we evaluated the a-wave amplitude of the fmERGs to determine the correlation between the functional and structural parameters. In the present study, we selected the b-wave as a functional measure because its amplitude is larger than the a-wave. In some cases, the a-wave was severely depressed while the b-wave amplitude was preserved and measurable. The selection of the b-wave did not enable us to directly compare the current with the previous data. However, because the b/a-wave amplitude ratio was unchanged throughout the study period, the changes in the b-wave amplitude would reflect alternations of the outer retinal layers directly related to the a-wave amplitude.

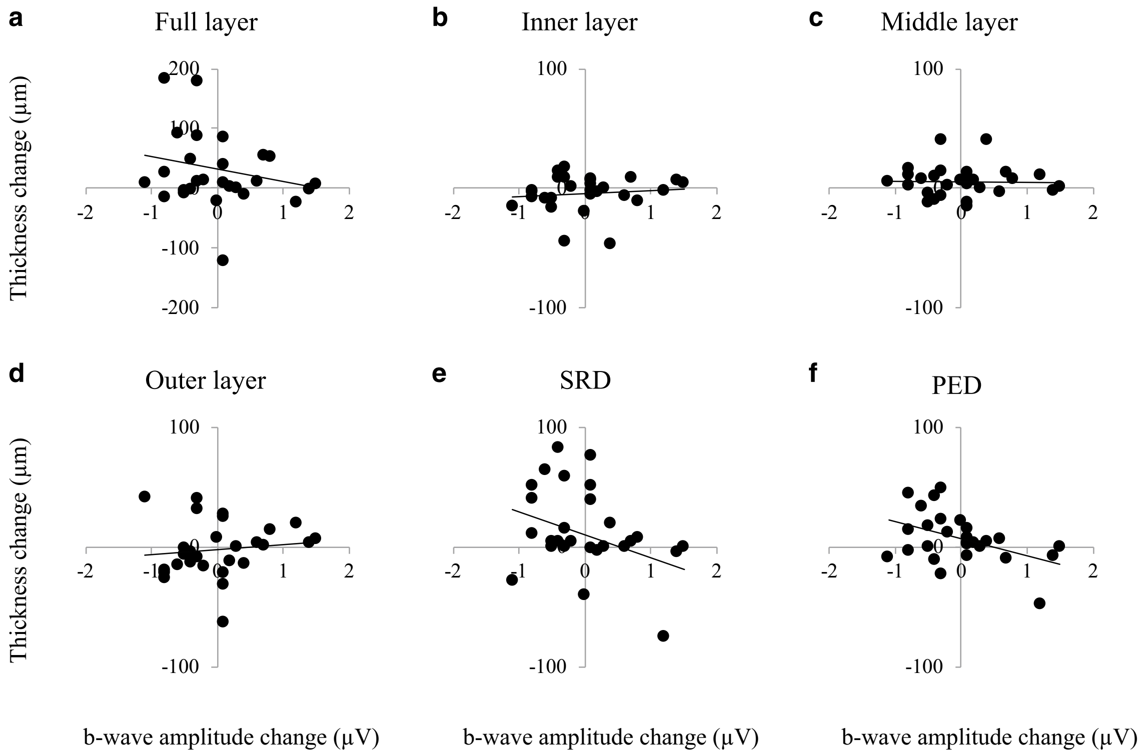

Fig. 6 Correlation between changes in parafoveal structures and b-wave amplitude of fmERG during PRN treatment period. Thicknesses of the full layer (**a**) and each retinal layer including the inner (**b**), middle (**c**) and outer retina (**d**), SRD (**e**) and PED (**f**) are plotted against the b-wave amplitudes. PRN: pro re nata

We evaluated the macular structure at only four retinal loci, viz., 1.2 mm from the fovea, in the parafoveal regions. Because the 15° stimulus spot illuminates a retinal area of approximately 3.0 mm in diameter, these four retinal loci are included in the stimulated area. Measuring the retinal thickness at numerous loci or constructing retinal maps of each layer would be a better way to investigate the relationships between structure and function. Further studies combined with development of new technology are needed to determine these relationships.

Conclusions

The structural parameters of the outer retina and subretina in the parafoveal region are correlated with the macular function measured by the fmERG at 12 months. In addition, improvements in the SRD affect the recovery of the macular function. Because recurrences of PEDs during the PRN period can deteriorate the macular function, control of the PEDs appears to be necessary to maintain good macular function in the long term.

Conflicts of interest T. Nishimura, None; S. Machida, None.

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