10.1515/chilat-2017-0016

ORIGINAL ARTICLE

Progression of Retinal Pigment Epithelium Atrophy in Patients with Long-Term Anti-Vegf Treatment for Exudative Age-Related Macular Degeneration

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Summary
Introduction. Age-related macular degeneration is the leading cause of visual impairment in developed world. The reason for using intravitreal injections of anti-vascular endothelial growth factor (VEGF) is to prevent choroidal neovascularization which is the main pathogenic mechanism for exudative age-related macular degeneration. Although injections may improve visual acuity, there are evidence showing association of anti-VEGF injections with progression of retinal pigment epithelium (RPE) atrophy.
Aim of the Study. The purpose of this study was to investigate the intravitreal anti-vascular endothelial growth factor impact on retinal pigment epithelium atrophy development and progression.
Material and methods. A single-centre retrospective study was conducted. Total 51 eyes of 39 patients with exudative age-related macular degeneration undergoing intravitreal anti-vascular endothelial growth factor therapy for 48 months. Heidelberg Spectralis Optical Coherence Tomography and fundus autofluorescence were used for evaluation of retinal pigment epithelium atrophy area and retinal thickness. Measurements were made manually. Best-corrected visual acuity (BCVA) measurements were taken from patient medical histories. For statistical analysis, IBM Statistical Package for the Social Sciences, version 23.0 was used.
Results. The average age of patients was 81.6 ± 6.7 years. After first year of intravitreal anti-VEGF therapy, retinal pigment epithelium atrophy area enlarged from baseline (from 1.91 ± 2.3 mm^2 to 2.74 ± 2.3mm^2, $p < 0.001$). The mean number of intravitreal anti-VEGF injections received in 48 months was 15.47 ± 5.14. There was a statistically significant correlation between total number of intravitreal injections and RPE atrophy ($R = 0.757$, $p < 0.001$). After first year of anti-VEGF therapy best-corrected visual acuity (decimals) was statistically improved from baseline (0.32 ± 0.26 to 0.37 ± 0.24, $p = 0.04$). However, despite significant improvement at first year, the further treatment contributed BCVA reduction.
Conclusions. Retinal pigment epithelium atrophy is a frequent finding in eyes with exudative age-related macular degeneration before and after anti-VEGF therapy. Our data show statistically significant association between total number of intravitreal anti-VEGF injections and retinal pigment epithelium atrophy area enlargement. Also there was statistically significant best-corrected visual acuity improvement after first year of anti-VEGF therapy.
Key words: age-related macular degeneration, retinal pigment epithelium, atrophy, best-corrected visual acuity

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of severe vision loss among adults aged 65 and over worldwide. (5.) It affects the central area of retina known as the macula which is responsible for the central field of vision. Retina consists of 10 layers of nerve cells and nerve fibers lying on a pigmented epithelial layer. (8.) Retinal pigment epithelium (RPE) is simple cuboidal cell layer located behind the photoreceptor cells and have many functions such as, ion and fluid transport, secretion of growth factors and protection against photooxidation and plays a major role in the pathogenesis of exudative AMD. (10.)

There are two forms of AMD, exudative age-related macular degeneration (wet or neovascular) and dry. Exudative AMD is characterized by neoangiogenesis in choroidea, often subsequently to intraretinal or subretinal exudation or hemorrhage. (1.,11.) The choroidal neovascularization leak into the macula, distorting it. Dry AMD is associated with drusen development. Drusen are lipid and protein composed deposits which are situated subretinal. Dry AMD can progress to wet AMD. (4.)

The mainstay treatment for exudative AMD is intravitreal injections of anti-vascular endothelial growth factor (VEGF). Ranibizumab and bevacizumab are the most commonly used anti-VEGF monoclonal antibodies. (13.) The aim of anti-VEGF injections is to prevent further angiogenesis and vasodilatation, reducing exudation and to potentially lead visual recovery. (2.) Although effective, the lasting of the effect is indefinite and often are required more intravitreal injections. (3.) The literature shows that there are signs of anti-VEGF treatment potentially increasing the possibility of RPE atrophy development and progression. (6.) Treatment also may have serious complications such as vitreous hemorrhage, cataract, retinal detachment or infections nevertheless these are rare. (13.,12.)

AIM OF THE STUDY

The aim of the study was to investigate if intravitreal anti-vascular endothelial growth factor injections can be associated with retinal pigment epithelium atrophy development and progression.

MATERIAL AND METHODS

A retrospective study was done in the Department of Ophthalmology of P. Stradins Clinical University Hospital. A total 51 eyes of 39 patients with exudative AMD who had received treatment with anti-VEGF and followed for 48 months were included. Eyes that received photodynamic therapy or laser treatment were excluded.

Were analysed best-corrected visual acuity (BCVA), RPE atrophy area and retinal thickness.

BCVA measurements were taken from patient medical histories and values were represented in decimals.

Heidelberg Spectralis Optical Coherence Tomography (OCT) fundus autofluorescence (FAF) was used for evaluation of RPE atrophy area. Measurements were manually made in square millimetres. (Figure 1.) Central retinal thickness was measured by OCT retinal cross-section and represented in micrometres. All measurements made before therapy and 12, 24 and 48 months undergoing anti-VEGF therapy.

Data management and statistical analysis were done with the IBM SPSS Statistics 23.

This study was approved by the local Ethics committee.

RESULTS

We analysed 51 eyes of 39 patients with exudative AMD, treated in our department for 48 months. Among them 38 (74.5%) were female and 13 (25.5%) male eyes. Right eyes were 26 (51%), left eyes 25 (49%). The mean age of the patients was 81.6 ± 6.7 years. The mean number of intravitreal anti-VEGF injections received in 48 months was 15.4 ± 5.14. Characteristics of patients are shown in Table 1.

There was a statistically significant correlation between total number of intravitreal injections and RPE atrophy ($R = 0.757$, $p < 0.001$). (Figure 2).

After first year of anti-VEGF therapy the mean RPE atrophy area was slightly increased from baseline (from 1.91 ± 2.3 mm^2 to 2.74 ± 2.3 mm^2, $p = 0.004$). RPE atrophy enlargement was observed also after 24 months and 48 months of anti-VEGF therapy (3.01 ± 2.46 mm^2 and 4.08 ± 3.62 mm^2, $p < 0.001$). The change of RPE atrophic area over 48 months after anti-VEGF treatment is shown in Figure 3.

Research indicates that after first two years of therapy RPE atrophic area progressed faster - progression rate in first 24 months was 1.34 ± 1.59 mm^2 and 1.92 ± 2.04 mm^2 per next two years. Heidelberg Spectralis OCT scan for RPE atrophy progression is shown in Figure 4.

Among 8 eyes without RPE atrophy at baseline, 7 eyes (87.5%) developed RPE atrophy at 12 months.

Mean best-corrected visual acuity (BCVA) (decimals) at the beginning of therapy was 0.32 ± 0.25. After twelve monthly anti-VEGF injections, BCVA was significantly improved from baseline (0.37 ± 0.24, $p = 0.04$). However, after essential improvement, we observed remarkable BCVA decreasing at month 24 and 48 (0.29 ± 0.23 and 0.28 ± 0.21). (Figure 5).

Mean retinal thickness before treatment was 394.94 ± 181.39 μm. After 12 months of treatment retinal thickness decreased to 304.24 ± 121.03 μm, which is significantly thinner than retinal thickness before therapy. Thickness reduction was noticed after 24 and 48 months of anti-VEGF therapy also (295.6 ± 112. 27 μm and 271.22 ± 104.01 μm). The change of retinal thickness over 48 months of anti-VEGF therapy is shown in Figure 6.

Complete characteristics of 48 month anti-VEGF treatment impact on RPE atrophy progression, BCVA and retinal thickness reduction is shown in Table 2.

DISCUSSION

Using data from Central Statistical Bureau of Latvia, it has been estimated that in 2017. in Latvia there was more than 388 thousand people over 65 years. (9.) That means our population have higher risk of age-related macular degeneration development and is relevant to be discussed.

Our study evaluated the quantitative changes of RPE atrophy in eyes with exudative AMD, and important enlargement of RPE atrophy was shown after anti-VEGF treatment. We found that after first year of anti-VEGF therapy BCVA improved significantly, reduction of retinal thickness was remarkable and there was observed RPE atrophy area progression.

A few publications have shown that anti-VEGF may exhibit the development and progression of RPE atrophy. For example, in the CATT trial which compared bevacizumab with ranibizumab, shown that both medications have quite similar effect, but in eyes that had monthly intravitreal injections comparison with as-needed injections, RPE atrophy progressed more. (6., 7.)

Despite several studies, still is unclear whether RPE atrophy that develops undergoing anti-VEGF treatment is a result from normal age-related macular degeneration progression or anti-VEGF therapy has a toxic effect on macula causing acceleration of RPE atrophy enlargement. (7.)

In our study we found a statistically significant improvement of BCVA after 12 months of anti-VEGF therapy, however, after further anti-VEGF therapy BCVA was with negative dynamic. The SEVEN-UP study shown that about 50% patients at the end of seven years anti-VEGF therapy had a loss of visual acuity by 15 letters due to RPE atrophy. (4.)

Anti-VEGF therapy is a gold standard and still is highly recommended to treat exudative AMD.

Although the aim of anti-VEGF therapy is to prevent further angiogenesis and vasodilatation, reducing exudation, approximately 25-35% of patients after intensive therapy still have evidence of active exudation on OCT and there are no significant changes in BCVA. (3.) For that reason, we should have to discuss if it is

appropriate to try reduce retinal exudation if there are no evidence of BCVA improving.

CONCLUSIONS

Retinal pigment epithelium atrophy progresses in eyes with exudative AMD during anti-VEGF therapy. The higher number of total injections correlate with extensive area of RPE atrophy. We found that progression of RPE atrophy was more rapid during third and fourth year of therapy comparing with first two years. Our results show that the intravitreal anti-VEGF therapy have a significant improvement of BCVA and reduction of retinal thickness after first twelve months. After next two years of therapy we observed decreasing of BCVA and inconsequential changes of retinal thickness.

Conflict of interest: None

REFERENCES

1. Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration // Neuron. 2012;75(1):26-39
2. Ba J, Peng R-S, Xu D, et al. Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis // Drug Design, Development and Therapy. 2015;9:5397-5405
3. Broadhead G.K, Hong T, Chang A. Treating the untreatable patient: current options for the management of treatment-resistant neovascular age-related macular degeneration // Acta Ophthalmologica, 2014; 92:8 713-723
4. Enslow R, Bhuvanagiri S, Vegunta S, Cutler B, Neff M, Stagg B. Association of Anti-VEGF Injections with Progression of Geographic Atrophy // Ophthalmology and Eye Diseases. 2016;8:31-32
5. Ferris FL. Senile macular degeneration: review of epidemiologic features // Am J Epidemiol, 1983; 118:132–151
6. Gemenetzi M, Lotery AJ, Patel PJ. Risk of geographic atrophy in age-related macular degeneration patients treated with intravitreal anti-VEGF agents. Eye. 2017;31(1):1-9.
7. Ramenaden E, Rosenfeld P. Can Anti-VEGF Cause GA in Wet AMD? // Available: http://www.retina-specialist.com/article/can-antivegf-cause-ga-in-wet-amd
8. Renu Jogi. Basic Ophthalmology, 4th Edition. New Delhi: Jaypee Brothers Medical Publishers (P); 2009; 1–9
9. Resident population by major age group at the beginning of the year. Available: http://data.csb.gov.lv/pxweb/en/Sociala/Sociala__ikgad__iedz__iedzskaits/IS0022.px/?rxid=cd
10. Sparrrow JR, Hicks D, Hamel CP. The Retinal Pigment Epithelium in Health and Disease // Current molecular medicine. 2010;10(9):802-823
11. Veritti D, Sarao V, Lanzetta P. Neovascular age-related macular degeneration // Ophthalmologica, 2012; 1:11-20
12. Xu Y, Tan CS. Safety and complications of intravitreal injections performed in an Asian population Singapore // Int Ophthalmol, 2017; 37(2):325–332
13. Yorston D. Anti-VEGF drugs in the prevention of blindness // Community Eye Health. 2014;27(87):44-46

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Table 1. Baseline characteristics of patients

Variables	N = 51 eyes (39 patients)
Age	81.6 ± 6.7
Gender, n (%) Women Men	 38 (74.5%) 13 (25.5%)
Area of RPE atrophy (mm^2)	1.91 ± 2.3
BCVA (decimals)	0.31 ± 0.26
Retinal thickness (μm)	394.94 ± 181.39

Table 2. The changes of RPE atrophy, BCVA and retinal thickness over anti-VEGF therapy

	RPE atrophy (mm^2)	**BCVA**	**Retinal thickness** (μm)
12 months	+ 0.82 ± 1.5	+ 0.06 ± 0.19	- 90.7 ± 140.83
24 months	+ 0.52 ± 0.59	- 0.08 ± 0.16	- 8.64 ± 112.31
48 months	+ 1.92 ± 2.04	- 0.01 ± 0.11	- 24.38 ± 59.5

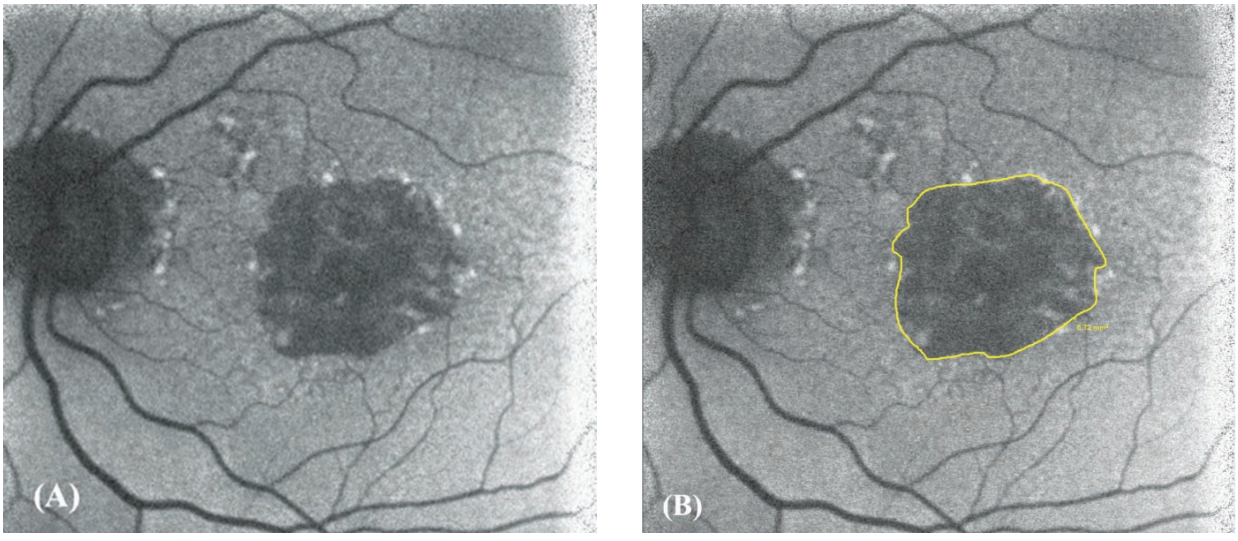

Fig. 1. Fundus autofluorescence (FAF) obtained with Heidelberg Spectralis OCT of RPE atrophic area
(A) In FAF atrophy shows as well-demarcated hypofluorescent area. (B) RPE atrophy is marked on this representative scan (yellow contour).
Images from Ophthalmology department of Pauls Stradins Clinical University Hospital

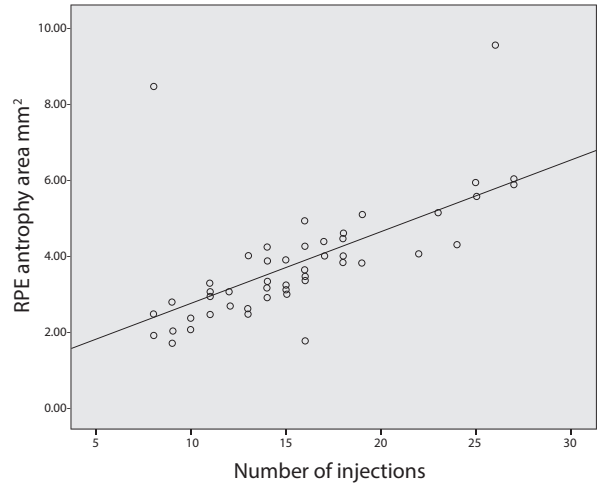

Fig. 2. Correlation between total number of intravitreal injections and retinal pigment epithelium atrophy

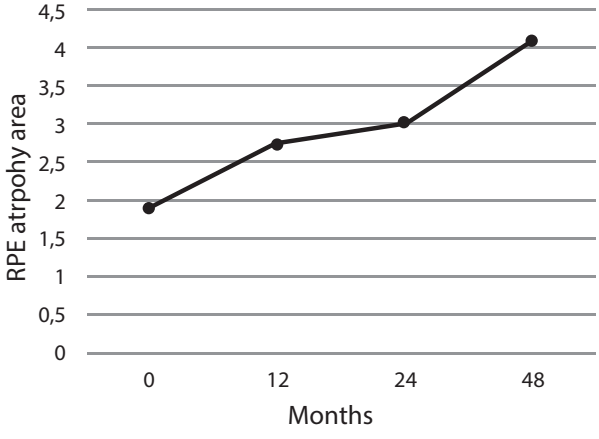

Fig. 3. The progression of retinal pigment epithelium atrophic area (mm²) over time after anti-vascular endothelial growth factor treatment

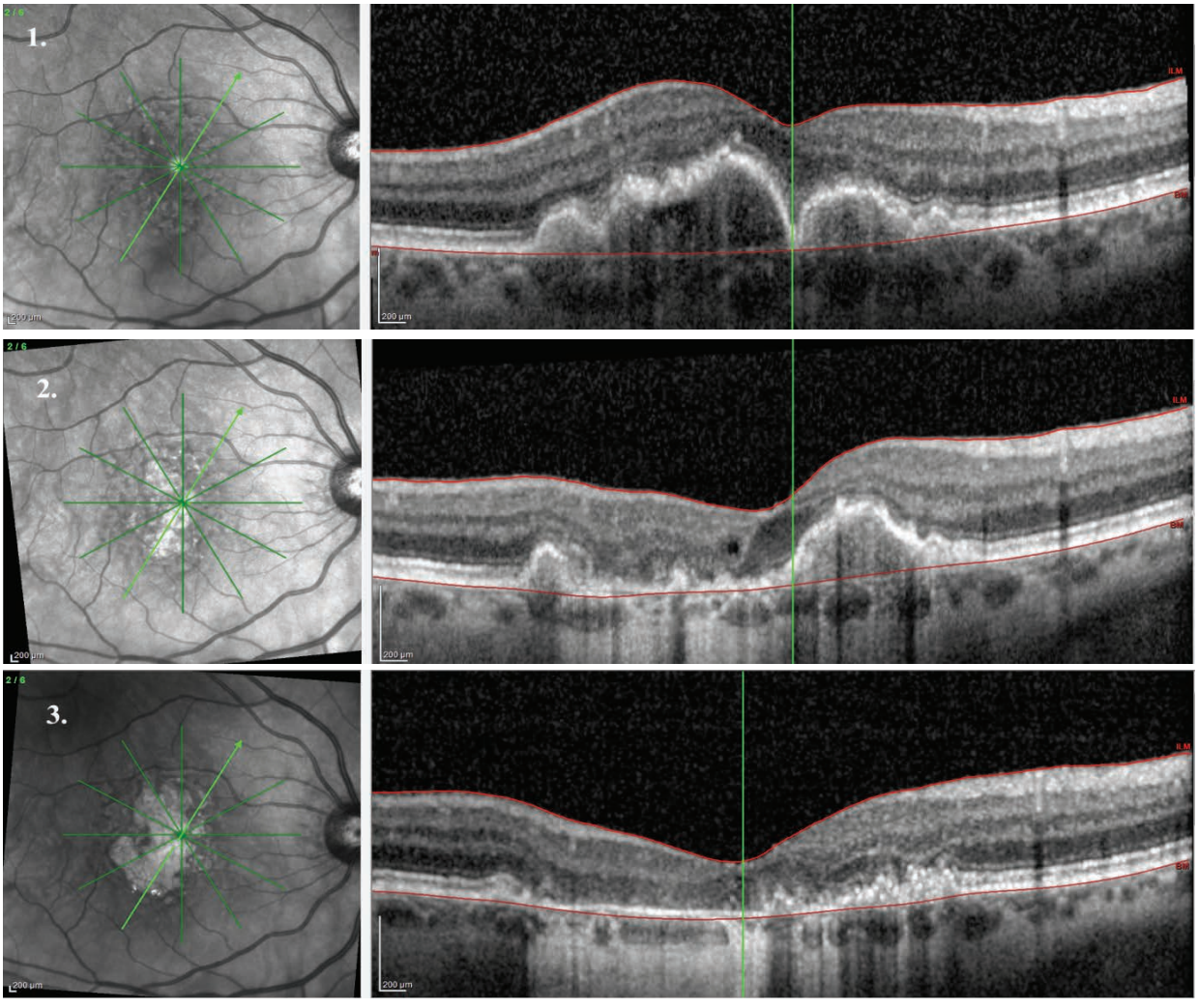

Fig. 4. Heidelberg Spectralis OCT scan of typical RPE atrophy progression
Retinal pigment epithelium atrophy appears as pigmentary hyperreflective area with sharp margins. In the retinal cross-section atrophy reveals as choroidal signal enhancement. (1.) At baseline, (2.) after 12 months of anti-VEGF therapy, (3.) after 48 months of anti-VEGF therapy.
Images from Ophthalmology department of Pauls Stradins Clinical University Hospital.

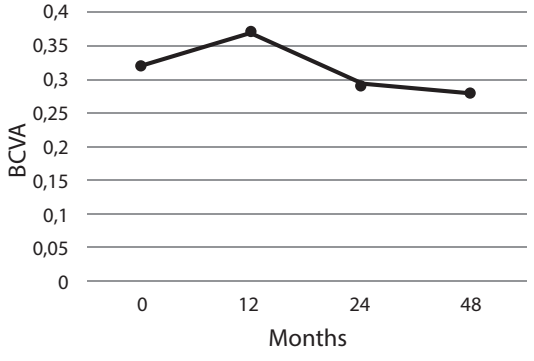

Fig. 5. The changes of best-corrected visual acuity (decimals) over time after anti-vascular endothelial growth factor treatment

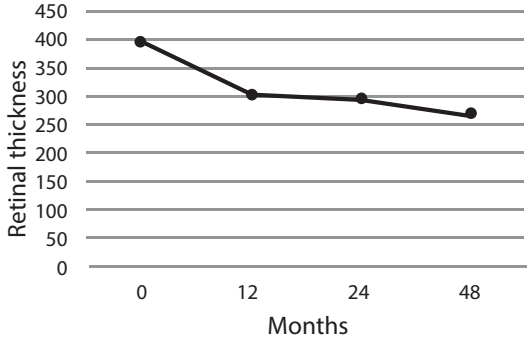

Fig. 6. The changes of retinal thickness (µm) over time after anti-vascular endothelial growth factor treatment