Is There a Relationship Between Use of Anti-Vascular Endothelial Growth Factor Agents and Atrophic Changes in Age-Related Macular Degeneration Patients?

*Süleyman Kaynak*, **Mahmut Kaya**, **Derya Kaya**

*Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
**Dokuz Eylül University Faculty of Medicine, Department of Geriatric Medicine, İzmir, Turkey

Abstract

Choroidal neovascularization due to age-related macular degeneration (AMD) is currently treated successfully with anti-vascular endothelial growth factor (VEGF) intravitreal agents. Emerging evidence suggests that anti-VEGF treatment may potentially increase development of geographic atrophy. However, there is not yet direct proof of a causal relationship between geographic atrophy and use of anti-VEGF agents in nAMD. The aim of this review is to discuss the evidence concerning the association between anti-VEGF therapy and progression of geographic atrophy.

Keywords: Anti-VEGF agents, geographic atrophy, age-related macular degeneration

Introduction

Intravitreal anti-vascular endothelial growth factor (VEGF) application has been the most effective treatment method in recent years for neovascular age-related macular degeneration (AMD).¹²³ The common feature of the multicenter studies conducted in this area with different agents and for different purposes is that they first determined the efficacy and safety of these agents. In the MARINA and ANCHOR trials, monthly ranibizumab injections preserved visual acuity and maintained vision level, and this finding has been clearly demonstrated in evidence-based, controlled comparative studies.¹² Two main points have recently been raised regarding the safety of anti-VEGFs. The first concern is local side effects such as endophthalmitis, vitreal hemorrhage, or retinal detachment, and the second is systemic side effects, especially cerebrovascular events. However, studies of these extremely rare adverse events showed that the use of these agents was not significantly associated with the likelihood of developing such complications.¹²³⁴⁵

Retrospective analyses of multicenter studies have provided new and interesting findings. One example is evidence from the CATT³ trial which suggests a relationship between long-term anti-VEGF therapy and the development of geographic atrophy. The IVAN⁴ and HARBOR⁶ trials were also retrospectively analyzed in terms of this possible relationship and reported suspicious findings similar to those found in the CATT trial.³⁴⁵⁶⁷⁸

Therefore, one of the most important questions of recent times is whether late geographic atrophy is really more prevalent in patients with long-term anti-VEGF use, and if so, what role the anti-VEGF agents play in the development of geographic atrophy.

Geographic Atrophy: Natural Course

Geographic atrophy is an age-associated pathology whose etiopathogenesis involves complex processes.⁷⁸ The main factor is an atrophic process that begins in the retinal pigment epithelium (RPE) and choriocapillaris.⁷ Genetics and aging

Address for Correspondence: Süleyman Kaynak MD, Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
Phone: +90 232 464 49 49 E-mail: skaynak@retina-gm.com ORCID-ID: orcid.org/0000-0001-5587-7238
Received: 01.12.2016 Accepted: 10.07.2017
©Copyright 2018 by Turkish Ophthalmological Association
Turkish Journal of Ophthalmology, published by Galenos Publishing House.
are the main risk factors. Parallel to senescence of retinal pigment epithelial cells, lipofuscin begins to accumulate in the cytoplasm due to slowing lysosomal activities, resulting in a vicious cycle. Metabolism slows with aging, especially lysosomal metabolism, and phagocytosed lipid-rich material does not dissolve, accumulating as a result. These deposits, particularly of lipofuscin, increase oxidative stress and accelerate aging. This vicious cycle leads to faster atrophy and RPE cell loss. Lipofuscin increases oxidative stress and RPE cell apoptosis. In geographic atrophy, autofluorescence imaging in particular shows RPE cells that are still viable but lipofuscin-laden concentrated along the margin of the advancing atrophic zone. After cell loss, this vicious cycle leads to faster atrophy and RPE cell loss. This phenomenon demonstrated by fundus evaluation of the CATT15 study revealed that geographic atrophy may be associated with anti-VEGF agents. A retrospective evaluation of the relationship between geographic atrophy and anti-vascular endothelial growth factor use is summarized in Table 1.

Table 1. Evaluation of the relationship between geographic atrophy and anti-vascular endothelial growth factor use according to the literature

| Patients with wet AMD who receive intravitreal anti-VEGF injections develop geographic atrophy in later stages. This process also occurs in the natural course of the disease. However, there is some debate regarding the extent to which this atrophy is related to the use of the agent. |
|---|
| No difference was observed between the agents used (bevacizumab and ranibizumab) in terms of geographic atrophy development. It can be said that the agents are not a risk factor. There is no data on aflibercept in this respect. |
| Ranibizumab dosage (0.5 or 2 mg) was not associated with incidence of geographic atrophy development. In other words, ranibizumab dose was not considered a risk factor. |
| Patients with atrophy in the fellow eye have been shown to have a slightly higher risk of atrophy in the presence of intraretinal fluid in the treated eye. |
| Patients with baseline geographic atrophy, the geographic atrophy tends to expand more rapidly in cases with geographic atrophy in the fellow eye, wet AMD, or scar. |
| The results of HARBOR indicated that risk of developing geographical atrophy was lower in the presence of subretinal fluid, suggesting that extreme efforts to eliminate fluid could be abandoned. |
| In the HARBOR trial, when patients treated according to a PRN regimen were analyzed separately based on number of injections, a greater number of injections was associated with lesser extent of atrophic change. This result contradicts other findings that indicate monthly injection is disadvantageous compared to PRN. For example, patients receiving 7-12 injections over 2 years of PRN treatment had a 29% incidence of atrophy, while the incidence was 18% and 19% respectively for patients who received 13-18 injections and >18 injections (nearly equivalent to monthly). |
| In subanalysis of the CATT and IVAN trials, comparison of patients treated with monthly and PRN administration showed that the average rate of atrophy development was lower in the PRN group. |

Although the monthly and PRN ranibizumab groups did not differ significantly in terms of foveal atrophy development, the difference in extrafoveal atrophy rate was statistically significant. It was determined in the CATT15 study that the important common risk factors among patients who developed geographic atrophy were vision level of 0.1 or lower, retinal angiomatous proliferation, geographic atrophy in the fellow eye, and baseline intraretinal fluid. Conversely, factors associated with lower risk included blocked fluorescein, subretinal fluid thickness of 25 μm or more, subretinal tissue complex thickness of 275 μm or greater, and the presence of vitreoretinal adhesions. The CATT15 study compared the 1- and 2-year results of treatment with ranibizumab and bevacizumab. Although the patients in the ranibizumab group showed a higher risk of developing geographic atrophy, there was no difference in incidence between the groups at the end of the treatment regimen. Geographic atrophy was extrafoveal in the majority of patients.

In contrast to the CATT, the 2-year results of the IVAN trial did not reveal a significant difference in geographic atrophy rates between patients treated with ranibizumab and those treated with bevacizumab (28% with ranibizumab, 31.2% with bevaczumab, p=0.46). When the results of the CATT15 and IVAN trial were interpreted together, the relationship between anti-VEGF use: Results of Multicenter Studies

Significant visual gains can be achieved in AMD patients with choroidal neovascularization (CNV) with long-term intracocular injection of numerous anti-VEGF agents. However, there is debate in the literature regarding whether the geographic atrophy seen during long-term follow-up in these patients, who had received many anti-VEGF injections at high frequency, was a result of the natural course of the disease or was associated with the anti-VEGF molecules used. Our current understanding of the relationship between geographic atrophy and anti-VEGF use is summarized in Table 1.

It was noted with the CATT15 study that geographic atrophy may be associated with anti-VEGF agents. A retrospective evaluation of the CATT15 study revealed that geographic atrophy had developed in 18.3% of the patients (187 of 1024 patients) at the end of 2 years. It was also observed in the retrospective analysis that there was a difference between the monthly application and pro re nata (PRN) groups in terms of geographic atrophy. Of the patients who were administered monthly ranibizumab, 4.7% exhibited foveal atrophy and 21.1% extrafoveal atrophy at the end of year 2. These rates were 3.7% and 11.5%, respectively, in the patients who received ranibizumab PRN.
intravitreal agents and the development of geographic atrophy could not be proven definitively. However, the IVAN\(^4\) trial revealed a correlation between the development of geographical atrophy and the frequency of intravitreal anti-VEGF applications. At 2-year follow-up, the risk of developing geographic atrophy was reported as 34\% with monthly intravitreal administration and 26\% with PRN administration. The methods used to evaluate geographic atrophy in the CATT\(^5\) and IVAN\(^4\) studies were different. There was no agreement or consistency between the studies regarding the methodology of atrophy assessment.

In the CATT\(^5\) trial, fundus fluorescein angiography (FFA) and the studies regarding the methodology of atrophy assessment. There was no agreement or consistency between the IVAN\(^4\) study, atrophic areas were visualized with FFA, color fundus imaging were used to detect atrophic areas. In the CATT\(^5\) and IVAN\(^4\) trials. HARBOR\(^6\) is a Phase 3 trial in which OCT, and their boundaries can be determined.

In brief, despite different assessment techniques, both the 2-year results of CATT\(^5\) and the late subanalyses performed after conclusion of the IVAN\(^4\) trial showed that treatment was associated with higher incidence of geographic atrophy, but it was usually extrafoveal and did not affect vision significantly. They also indicated that the agents used were not influential in this phenomenon but that administration regimen may have an effect, with a PRN regimen being more favorable than monthly injections. Subanalysis of the HARBOR\(^6\) trial was similar to the CATT\(^5\) and IVAN\(^4\) trials. HARBOR\(^6\) is a Phase 3 trial in which the 2-year efficacy results of two different doses of ranibizumab (0.5 mg and 2 mg) with two different administration regimens (monthly/PRN) were evaluated in treatment-naive wet AMD patients with active subfoveal CNV (\(n=1097\)). Geographic atrophy was assessed using FFA and color fundus images at 3, 12, and 24 months. Similar to the IVAN\(^4\) trial, baseline areas of atrophy were also taken into account in the HARBOR\(^6\) trial. Included in the areas of geographic atrophy were depigmented areas with prominent borders and increased visibility of choroidal vessels, areas with diameters greater than \(\geq 250\ \mu\text{m}\), and attached, flat areas with prominent borders on FFA. However, atrophic areas with RPE tears were excluded. In the HARBOR\(^6\) trial, areas of atrophy adjacent to and nonadjacent to CNV were separately identified and evaluated. Lesions adjacent to CNV were especially included to achieve comparable results to the CATT\(^5\) and IVAN\(^4\) trials. In the HARBOR\(^6\) study, the incidence of atrophy in the eyes with no detectable atrophy at baseline was 29\% according to results at 24 months. Based on this finding, there were no significant differences in atrophy incidence when compared with the CATT\(^5\) (20\%) and IVAN\(^4\) (28\%) trials. In the CATT\(^5\) trial, patients with baseline atrophy in the initial examination were not included in the evaluation. For this reason, the incidence of atrophy was found to be lower compared to the IVAN\(^4\) and HARBOR\(^6\) trials, which included patients with baseline atrophy. IVAN\(^4\) and HARBOR\(^6\) are more comparable in terms of patient groups, and the total incidence of atrophy, including existing (baseline) and newly developed atrophy, was equivalent at 28\% and 29\% respectively. In a subgroup analysis of the 5-year results of the CATT\(^5\) trial, the incidence of geographic atrophy was found to be 38\%. The development of geographic atrophy was common and risk factors present at 2 years persisted at 5 years. The most important risk factors at start of treatment for the development of geographic atrophy were advanced age, poor visual acuity, widespread CNV, retinal angiomatous proliferation, geographic atrophy in the fellow eye, and intraretinal fluid. Thick subretinal tissue complex and presence of subretinal fluid were less associated with development of geographic atrophy. Incidence rates of geographic atrophy in post hoc analyses of the IVAN, CATT, and HARBOR trials are summarized in Table 2.

These findings point to two major conclusions from the HARBOR\(^6\) trial. One of these is that the agent used was not

| Table 2. Comparison of the results of multicenter, randomized clinical trials showing the incidence of geographic atrophy related to anti-vascular endothelial growth factor use in wet age-related macular degeneration |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patient number (n) | Anti-VEGF agent | Treatment regimen | Professional experience | Method |
|----------------|----------------|----------------|----------------|----------------|
| Chakravarthy et al.\(^1\) (IVAN study) | Bevacizumab | 1.25 mg/PRN | 24 months | FFA, OCT, Color fundus photograph |
| 525 | Ranibizumab | 0.5 mg | | Bevacizumab 51% Ranibizumab 28% |
| Grunwald et al.\(^4\) (CATT study 2-year results) | Bevacizumab | 1.25 mg | 2 years | FFA, Color fundus photograph |
| 1024 | Ranibizumab | 0.5 mg/PRN | | 18% |
| Sarraf et al.\(^4\) (HARBOR study) | Ranibizumab | 0.5 mg/PRN | 24 months | FFA, Color fundus photograph |
| 1097 | 2 mg/PRN | PED (+) 29% PED (+) 32% |
| Grunwald et al.\(^4\) (CATT study 5-year results) | Bevacizumab | 1.25 mg | 5 years | FFA, Color fundus photograph |
| 517 | Ranibizumab | 0.5 mg/PRN | | 38% |

GA: Geographic atrophy, FFA: Fundus fluorescein angiography, OCT: Optical coherence tomography, PED: Pigment epithelial detachment, PRN: Pro re nata, VEGF: Vascular endothelial growth factor
influential on the development of atrophy, as in the CATT\textsuperscript{15} and IVAN\textsuperscript{2} trials. In the HARBOR\textsuperscript{3} trial, it was observed that the dose (0.5 mg vs. 2 mg) and number (monthly vs. PRN) of ranibizumab injections administered were not associated with rates of atrophy development.

Another important issue that must be considered in relation to geographic atrophy development is the effects of atrophic changes on visual acuity. Especially in the CATT\textsuperscript{15} trial, it may have been difficult to notice these extrafoveal atrophic areas if the retrospective analysis had not been performed, and since most of them had no effect on visual acuity, it is understandable that they could be overlooked by a researcher. In subanalysis of the study, no statistically significant difference was detected in the comparison of visual changes in patients with and without atrophy.

**Conclusion**

In conclusion, retrospective analyses of the CATT\textsuperscript{15,16}, IVAN\textsuperscript{3}, and HARBOR\textsuperscript{3} trials suggest that long-term intravitreal anti-VEGF therapies increase geographic atrophy in wet AMD patients. Even if this is the case, however, considering that 80% of these atrophic changes are extrafoveal and do not directly affect visual acuity, wet AMD patients should nevertheless be treated with adequate duration and frequency despite this possibility. As observed in the MARINA\textsuperscript{2} and ANCHOR\textsuperscript{3} trials, treatment yields visual gains of over 20 letters, compared to the loss of 14 letters in the sham group, which reflects the natural disease course. Even if atrophy does develop, the difference in letters gained between the patients with and without atrophy is 2.4 letters at 24 months. In light of these findings, it remains to be clarified whether the areas of geographic atrophy seen after anti-VEGF therapy in wet AMD are associated with the natural course of the disease or emerge as a result of the anti-VEGF molecules used in treatment. Regardless, considering the approximately 20-letter gain achieved over a 2-year period in these patients compared to the natural course, we believe these therapies are still indispensable for the treatment of wet AMD.

**Ethics**

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Süleyman Kaynak, Concept: Süleyman Kaynak, Design: Süleyman Kaynak, Mahmut Kaya, Data Collection or Processing: Süleyman Kaynak, Mahmut Kaya, Derya Kaya, Analysis or Interpretation: Süleyman Kaynak, Mahmut Kaya, Literature Search: Mahmut Kaya, Derya Kaya, Writing: Süleyman Kaynak, Mahmut Kaya, Derya Kaya.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

---

**References**

1. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419-1431.
2. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T, ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR Study. Ophthalmology. 2009;116:57-65.
3. CATT Research Group. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364:1897-1908.
4. Chakravarty U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Callender LA, Reeves BC, IVAN study investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013;382:1258-1267.
5. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Mélia M, Piatnicki DJ, Sun JK, Beck RW, Afibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372:1193-1203.
6. Sarraf D, London NJ, Khurana RN, Dugel PJ, Gune S, Hill L, Tsouni L. Ranibizumab Treatment for Pigment Epithelial Detachment Secondary to Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of the HARBOR Study. Ophthalmology. 2016;123:2213-2224.
7. Clemmons TE, Milton RC, Klein R, Seddon JM, Ferris FL 3rd, Age-Related Eye Disease Study Research Group. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS): AREDS report no. 19. Ophthalmology. 2005;112:533-539.
8. Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. Risk factors for choroidal neovascularization and geographic atrophy in the Complications of Age-related Macular Degeneration Prevention Trial. Ophthalmology. 2008;115:1474-1479.
9. Gemenetzii M, Lotery AJ, Patel PJ. Risk of geographic atrophy in age-related macular degeneration patients treated with intravitreal anti-VEGF agents. Eye (Lond). 2017;31:1-9.
10. Barraza E, Brossas JY, Courtois Y, Tréton JA. Accumulation of mitochondrial DNA deletions in human retina during aging. Invest Ophthalmol Vis Sci. 1996;37:384-391.
11. Chen H, Lukas TJ, Du N, Suyeoka G, Neufeld AH. Dysfunction of the retinal pigment epithelium with age: increased iron decreases phagocytosis and lysosomal activity. Invest Ophthalmol Vis Sci. 2009;50:1895-1902.
12. Ach T, Tolstik E, Messinger JD, Zarubina AV, Heintzmann R, Curcio CA. Lipofuscin redistribution and loss accompanied by cytосkeletal stress in retinal pigment epithelium of eyes with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2015;56:3242-3252.
13. Abdelalaram A, Del Priore L, Zarbin MA. Druen in age-related macular degeneration: pathogenesis, natural course, and laser photocoagulation-induced regression. Surv Ophthalmol. 1999;44:1-29.
14. Saint-Geniez M, Kurihara T, Sekiyama E, Maldonado AE, D’Amore PA. An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. Proc Natl Acad Sci U S A. 2009;106:18751-18756.
15. Grunwald JE, Daniel E, Huang J, Ying GS, Maguire MG, Toth CA, Jaffe GJ, Fine SL, Bliod B, Klein ML, Martin AA, Hagstrom SA, Martin DF, CATT Research Group. Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2014;121:150-61.
16. Grunwald JE, Pastilli M, Daniel E, Ying GS, Pan W, Jaffe GJ, Toth CA, Hagstrom SA, Maguire MG, Martin DF, Comparison of Age-Related Macular Degeneration Treatments Trials Research Group. Incidence and Growth of Geographic Atrophy during 5 Years of Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology. 2017;124:97-104.