

# Association of Anti-VEGF Injections with Progression of Geographic Atrophy



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**ABSTRACT:** Age-related macular degeneration (AMD) is one of the leading causes of blindness in developed countries in people over the age of 60 years. One of the forms of advanced AMD is wet AMD. Wet AMD is a result of leakage and bleeding from abnormal neovascularization. The principal treatment for wet AMD is intravitreal anti-VEGF injections. A second form of advanced AMD is geographic atrophy (GA). GA refers to large areas of retinal pigment epithelium loss. In the literature, there is some concern that anti-VEGF injections administered to treat wet AMD may be associated with progression of GA. This review discusses evidence suggesting the association of anti-VEGF injections with progression of GA.

**KEYWORDS:** macular degeneration, neovascularization, geographic atrophy, anti-VEGF treatment

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## Introduction

Age-related macular degeneration (AMD) is a retinal disease associated with aging that affects the macula, which leads to gradual or sudden loss of central vision. The two principal types of AMD are wet and dry AMD. Wet AMD occurs when unstable blood vessels grow and extend from the choroid in a process called choroidal neovascularization (CNV) and leak into the macula. This leakage causes the macula to become distorted, resulting in vision loss. The primary treatment for CNV is anti-VEGF intravitreal injections. Anti-VEGF injections have been used to inhibit the formation of new blood vessels behind the retina to protect against leakage. Dry AMD is associated with the development of drusen. Drusen are subretinal deposits composed primarily of lipid and protein that enlarge with aging.

Geographic atrophy (GA) is an advanced form of dry AMD.<sup>1</sup> GA is the loss of an area of the retinal pigment epithelium (RPE). RPE is essential for vision as it maintains the health of the retina by transporting nutrients and ions, secreting growth factors, and protecting against photooxidation. The proposed sequence of events leading to GA is the progression of large drusen to hyperpigmentation, followed by regression of the drusen, hypopigmentation, and ultimately RPE cell death, leading to atrophic area of retina underlying choriocapillaris.<sup>2</sup> Macrophages are often seen in areas of GA, phagocytosing pigment and debris, resulting in the death of normal cells.<sup>1</sup> This evolution of GA can be longer than six years.<sup>3</sup>

## Evidence Showing Association of Anti-VEGF Injections with Progression of GA

Several publications have shown that patients with wet AMD who are receiving anti-VEGF injections may exhibit progression of GA during the course of treatment.<sup>3,4</sup> For example, the SEVEN-UP study observed GA progression in AMD patients treated with ranibizumab. SEVEN-UP is a follow-up study that followed up 65 patients who received ranibizumab treatment from MARINA, ANCHOR, and HORIZON cohort studies for treating AMD, over a mean of 7.4 years. In this study, about 50% of the patients had a loss of visual acuity by 15 letters at the end of seven years mainly due to GA.<sup>4</sup> Even though these patients had other anatomic changes such as macular thinning, subfoveal fibrosis, and subretinal fluid, these factors did not make a significant difference in the functional outcome of visual acuity. Even though this study evaluated the effects of one anti-VEGF drug (Lucentis), it still highlighted the importance of studying the side effect of GA due to its significant impact on the visual acuity of patients treated with anti-VEGF therapy.

However, these studies were not designed to evaluate the question of whether or not the anti-VEGF treatment was a risk factor for progression of the GA. The primary evidence suggesting that receiving more anti-VEGF injections is associated with GA progression comes from retrospective analysis of the Comparison of Age-Related Macular degeneration Treatment Trial (CATT).<sup>5</sup>

The CATT is a randomized clinical trial that showed that out of 1185 participants who were treated with ranibizumab



or bevacizumab (both are anti-VEGF drugs), 156 patients developed GA at the end of the second year.<sup>5</sup> The study found that even after taking into account several baseline risk factors for GA, patients treated with ranibizumab still had both higher GA area enlargement from the initial lesion and GA incidence than those treated with bevacizumab. The study also found that patients treated with monthly anti-VEGF treatment had higher GA progression rate than as needed treatment.

A cohort study by Grunwald et al showed that the two factors that were associated with highest GA incidence were the use of ranibizumab compared with bevacizumab and monthly anti-VEGF treatment, which confirms the previous findings of CATT.<sup>6</sup> This is further confirmed by the findings from the alternative treatments to inhibit VEGF in the age-related choroidal neovascularization randomized clinical trial in which patients on monthly anti-VEGF therapy had higher incidence of GA compared with those on as needed treatment.<sup>7</sup>

## Discussion

Understanding the association between anti-VEGF treatment and GA progression has important clinical implications, given the large number of patients receiving anti-VEGF injections. The only publications that we identified suggesting this association were retrospective analyses looking at the CATT trial and IVAN trial. Further evaluation of this question is necessary. While multiple studies have clearly shown that anti-VEGF treatment improves visual outcomes,<sup>8,9</sup> perhaps reduced dosing or as needed dosing could reduce the rate of GA development. It was also found that ranibizumab was associated with higher GA incidence compared with bevacizumab. Perhaps, it could be due to the fact that ranibizumab was found to be more effective in drying out the retina than bevacizumab.<sup>10</sup> However, further research is needed to evaluate the effect of dosing and the type of anti-VEGF therapy on GA incidence.

While there is still ongoing research on the mechanism of the cause of GA, one of the reasons for GA could be due to the drastic reduction of VEGF from anti-VEGF therapy. It was found that RPE-derived VEGF is necessary for maintenance of choriocapillaris and the absence of specific VEGF isoforms results in retinal degeneration similar to GA in the knockout mice.<sup>11</sup> However, as this study is limited to VEGF isoforms in mice, further research is needed to confirm similar results in humans.

While there are currently more clinical studies such as the RIVAL study looking at the association of GA and anti-VEGF therapy, more clinical research is needed to further understand this association.<sup>12</sup> We suggest future clinical studies include control groups not treated with anti-VEGF therapy and to use more diverse testing techniques such as retinal fundus autofluorescence to further study and establish the link between anti-VEGF therapy and the GA progression. We also suggest future clinical studies take into account

the subtype of CNV the patient is being treated for when studying this association as certain subtypes of CNV are associated with higher risk of developing GA.<sup>13</sup> While we still recommend clinicians to use anti-VEGF therapy to treat AMD patients, we want them to be more cognizant of this possible association and give more importance to the different types of anti-VEGF therapy and dosing regimens when treating AMD patients, especially those already with GA.

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## Author Contributions

Wrote the first draft of the manuscript: RE, SV, SB, BC, MN. Contributed to the writing of the manuscript: RE, SB, SV, BC, MN. Agreed with manuscript results and conclusions: RE, SB, SV, BC, MN, BS. Jointly developed the structure and arguments for the article: RE, SV, BS. Made critical revisions and approved the final version: BS. All the authors reviewed and approved the final manuscript.

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